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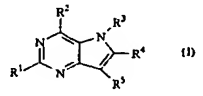
(54) Title: PYRROLOPYRIMIDINE DERIVATIVES USEFUL AS MODULATORS OF MULTIDRUG RESISTANCE



(I)

(57) Abstract: A compound which is a pyrrolopyrimidine of formula (I) wherein: R^1 is selected from R^9 and halogen; R^2 is NR^6R^7; R^3 is selected from H, C_1-C_6 alkyl which is unsubstituted or substituted and -(CH2) $_n$Ar; R^4 is selected from H, C_1-C_6 alkyl and -$(CH_2)_n$ Ar; or R^3 and R^4 form, together with the N and C atoms to which they are attached, a fused five-, six-, seven- or eight-membered N-containing saturated ring which is unsubstituted or substituted; R^5 is selected from CN, $C0_2R^9$,$C(O)NR^{10}R^{11}$, -$(CH_2)_nOH$, -$(CH_2)_nR^{10}R^n$, -C≡CH, -C(S)$NR^{10}R^{11}$, -$C(NH_2)$=NOR^9, -$C(R^9)$=NOR^9, -$C(NH_2)NH$, -$C(O)R^9$ and an unsaturated 5- or 6-membered heterocyclic group which contains 1, 2 or 3 heteroatoms selected from N, O and S and which is unsubstituted or substituted; R^6 and R^7, which are the same or different, are selected from C_1-C_6 alkyl which is unsubstituted or substituted, -$(CH_2)_nX$ and -$(CH_2)_nAr$; or R^6 and R^7 form, together with the nitrogen atom to which they are attached, a saturated five-, six-, seven- or eight-membered heterocyclic group which contains one nitrogen atom and 0 or from 1 to 3 additional heteroatoms selected from N, O and S, which is unsubstituted or substituted and which optionally contains one or two bridgehead atoms; $R^{10}$and R^{11}, which are the same or different, are selected from H, C_1-C_6 alkyl which is unsubstituted or substituted, -$(CH_2)_nC_3$-C_{10} cycloalkyl and -$(CH_2)_nAr$; or R^{10} and R^{11} form, together with the nitrogen atom to which they are attached, a saturated five or six membered heterocyclic group which contains a nitrogen atom and 0 or from to 3 additional heteroatoms selected from O, S and N, which is unsubstituted or substituted and which is optionally fused to a benzene ring which is unsubstituted or substituted; n is the same or different when more than one is present within a given substituent group and is 0 or an integer of from 1 to 6; X is selected from -CN, -$C0_2R^9$ and -$NR^{10}R^{11}$; R^9 is the same or different when more than one is present within a given substituent group and is selected from -H, -QAr, -$(CH_2)_nAr$, C_1-C_6 alkyl which is unsubstituted or substituted and -$(CH_2)_nC_3$-C_{10}cycloalkyl, wherein the cycloalkyl moiety is optionally fused to a benzene ring which is unsubstituted or substituted; Q is C_2-C_6 alkenylene or alkynylene; and Ar is an unsaturated C_6-C_{10} membered carbocyclic group or an unsaturated 5-11 membered heterocyclic group, which groups are unsubstituted or substituted; or a pharmaceutically acceptable salt thereof. These compounds have activity as inhibitors of MRP (multidrug resistant protein) and may thus be used to modulate multidrug resistance, for instance in potentiating the cytotoxicity of a chemotherapeutic agent.

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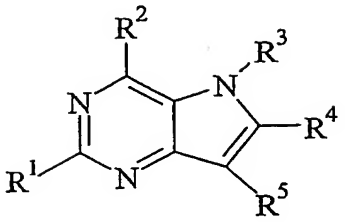
PYRROLOPYRIMIDINE DERIVATIVES USEFUL AS MODULATORS OF MULTIDRUG RESISTANCE

The present invention relates to compounds useful as modulators of multi-drug resistance (MDR), in particular resistance caused by over-production or expression of the multidrug resistance protein (MRP), to their preparation and to pharmaceutical and veterinary compositions containing them.

Resistance to a range of drugs is frequently encountered during chemotherapy of many types of cancer. Such resistance may develop during drug treatment or may be an inherent feature of a particular tumour type. This phenomenon termed multidrug resistance has been studied in the laboratory where drug-resistant cell lines, derived by exposure to a single chemotherapeutic agent, become cross-resistant to many structurally and functionally unrelated compounds to which they have not been previously exposed. The drugs encompassed by multidrug resistance include the anthracyclines, vinca alkaloids and epipodophyllotoxins.

Multidrug resistance is conferred by two different integral membrane proteins, the 170kDa P-glycoprotein (Pgp) and the 190kDa multidrug resistance protein (MRP). These proteins belong to the ATP-binding cassette (ABC) superfamily of transport proteins, but their primary structures are quite dissimilar, sharing only 15% amino acid identity. Nevertheless, MRP and Pgp confer resistance to a similar profile of drugs. Both proteins efflux doxorubicin, daunorubicin, vincristine, etoposide and paclitaxel. There are however significant quantitative differences. For example, whereas Pgp produces relatively high levels of resistance to paclitaxel, the reverse is true for MRP (Loe DW, Deeley RG, Cole SPC. (1996) Biology of the multidrug resistance-associated protein. *Eur J Cancer* 32A 945-957). In addition to these neutral or cationic drugs, MRP also transports a wide range of organic anions including glutathione conjugates, glucuronate conjugates, conjugated alkylating agents and some heavy metals (Cole SPC, Sparks KE, Fraser K. (1994) Pharmacological characterisation of multidrug resistant MRP-transfected human tumour cells. *Cancer Res* 54: 5902-5910).

It has now been found that a series of novel pyrrolopyrimidines have activity as inhibitors of MRP. Accordingly, the present invention provides a compound which is a pyrrolopyrimidine of formula (I):



(I)

wherein:

R^1 is selected from R^9 and halogen;

R^2 is NR^6R^7;

R^3 is selected from H, C_1-C_6 alkyl which is unsubstituted or substituted and $-(CH_2)_nAr$;

R^4 is selected from H, C_1-C_6 alkyl and $-(CH_2)_nAr$; or R^3 and R^4 form, together with the N and C atoms to which they are attached, a fused five-, six-, seven- or eight-membered N-containing saturated ring which is unsubstituted or substituted;

R^5 is selected from CN, CO_2R^9, $C(O)NR^{10}R^{11}$, $-(CH_2)_nOH$, $-(CH_2)_nNR^{10}R^{11}$, $-C\equiv CH$, $-C(S)NR^{10}R^{11}$, $-C(NH_2)=NOR^9$, $-C(R^9)=NOR^9$, $-C(NH_2)NH$, $-C(O)R^9$ and an unsaturated 5- or 6-membered heterocyclic group which contains 1, 2 or 3 heteroatoms selected from N, O and S and which is unsubstituted or substituted;

R^6 and R^7, which are the same or different, are selected from C_1-C_6 alkyl which is unsubstituted or substituted, $-(CH_2)_nX$ and $-(CH_2)_nAr$; or R^6 and R^7 form, together with the nitrogen atom to which they are attached, a saturated five-, six-, seven- or eight-membered heterocyclic group which contains one nitrogen atom and 0 or from 1 to 3 additional heteroatoms selected from N, O and S, which is unsubstituted or substituted and which optionally contains one or two bridgehead atoms;

R^{10} and R^{11}, which are the same or different, are selected from H, C_1-C_6 alkyl which is unsubstituted or substituted, $-(CH_2)_nC_3$-C_{10} cycloalkyl and $-(CH_2)_nAr$; or R^{10} and R^{11} form, together with the nitrogen atom to which they are attached, a saturated five or six membered heterocyclic group which contains a nitrogen atom and 0 or from 1 to 3 additional heteroatoms selected from O, S and N, which is unsubstituted or substituted and which is optionally fused to a benzene ring which is unsubstituted or substituted;

n is the same or different when more than one is present within a given substituent group and is 0 or an integer of from 1 to 6;

X is selected from -CN, $-CO_2R^9$ and $-NR^{10}R^{11}$;

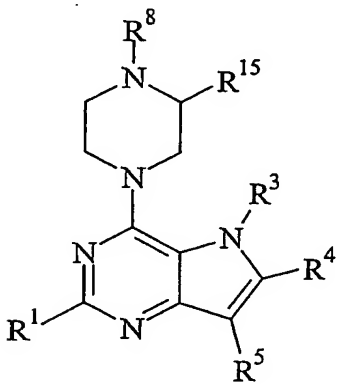
R^9 is the same or different when more than one is present within a given substituent group and is selected from -H, -QAr, $-(CH_2)_nAr$, C_1-C_6 alkyl which is unsubstituted or substituted and $-(CH_2)_nC_3$-C_{10}cycloalkyl, wherein the cycloalkyl moiety is optionally fused to a benzene ring which is unsubstituted or substituted;

Q is C_2-C_6 alkenylene or C_2-C_6 alkynylene; and

Ar is an unsaturated C_6-C_{10} membered carbocyclic group or an unsaturated 5-11 membered heterocyclic group, which groups are unsubstituted or substituted;

or a pharmaceutically acceptable salt thereof.

In a first preferred aspect of the invention the pyrrolopyrimidine is of formula (Ia):



(Ia)

wherein:

R^1, R^3, R^4 and R^5 are as defined above;

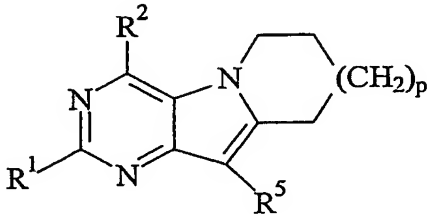
R^8 is selected from -H, $-(alk)_nY$, $-(alk)_nC(O)Y$, $-C(O)(alk)_nY$, $-C(O)NH(alk)_nY$, $-(alk)_nCHOH(alk)_nOY$, $-(alk)_nC{\equiv}CY$, $-(alk)_nOY$, $-S(O)_m(alk)_nY$ and $-(alk)_nC(O)NR^{10}R^{11}$ wherein m is 0, 1 or 2 and alk is C_1-C_6 alkylene which is unsubstituted or substituted by Y;

n, Q, R^{10} and R^{11} are as defined above;

Y is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, $NR^{10}R^{11}$ and Ar; and

R^{15} is H or C_1-C_6 alkyl.

In a second preferred aspect of the invention the pyrrolopyrimidine is of formula (Ib):



(Ib)

wherein R^1, R^2 and R^5 are as defined above and p is 0, 1, 2 or 3.

The pyrrolopyrimidines of formulae (I), (Ia) and (Ib) and their pharmaceutically acceptable salts are referred to herein as "compounds of the invention". In these compounds:

R^1 is typically H or Ar, preferably H.

R^3 and R^4 in formulae (I) and (Ia) are the same or different and are typically selected from H, CH_3, C_2H_5, isopropyl, cyclopentyl, phenyl, benzyl and $(CH_2)_2Ph$, or R^3 and R^4 form, together with the N and C atoms to which they are attached, a 5- 6- or 7-membered nitrogen containing ring. Preferably R^3 and R^4 form, together with the atoms to which they are attached, a 6-membered nitrogen-containing ring.

R^5 is typically CN, $C(O)NR^{10}R^{11}$, or an unsaturated 5 or 6 membered heterocycle which contains 1, 2 or 3 heteroatoms selected from N, O and S and which is unsubstituted or substituted. Preferably R^5 is CN, $C(O)NR^{10}R^{11}$ or thiazole which is unsubstituted or substituted.

R^8 in formula (Ia) is typically $-(alk)_nAr$, preferably $-(CH_2)_2Ar$.

R^{15} is typically H.

The parameter n is 0 or 1,2,3,4,5 or 6. Typically it is 0, 1,2 or 3.

A C_1-C_6 alkyl group is linear or branched. A C_1-C_6 alkyl group is typically a C_1-C_4 alkyl group, for example a methyl, ethyl, propyl, i-propyl, n-butyl, sec-butyl or tert-butyl group. A C_1-C_6 alkyl group is unsubstituted or substituted, typically by one or more groups selected from hydroxy-C_1-C_6 alkyl wherein the alkyl moiety is unsubstituted or substituted, halo-C_1-C_6 alkyl wherein the alkyl moiety is

unsubstituted or substituted, C_1-C_6 alkoxy, Ar, R^{12}, OR^{12}, SR^{12}, nitro, CN, halogen, -CO_2R^{12}, -$C(O)NR^{13}R^{14}$, -$NR^{12}C(O)R^{12}$, -$NR^{13}R^{14}$, -$(CH_2)_nO(CH_2)_nAr^2$, -$O(CH_2)_nC(O)NR^{13}R^{14}$, -$S(O)_2R^{12}$, -$N(C(O)R^{12})_2$, -$S(O)_2NR^{13}R^{14}$, $NR^{12}S(O)_2R^{12}$, R^9, -OR^9, -$(CH_2)_nNR^{10}R^{11}$, -$CH_2)C(O)NR^{10}R^{11}$, -$(CH_2)_nOR^9$, -$(CH_2)_nC(O)(CH_2)_nR^9$, -$(CH_2)_nC(O)NC(O)Ar^2$ and -$(CH_2)_nO(CH_2)_nAr^2$, wherein R^{12}, R^{13}, R^{14}, and Ar^2 are as defined below. Preferred substituents are hydroxy-C_1-C_6 alkyl, halo-C_1-C_6 alkyl, C_1-C_6 alkoxy, Ar, R^{12}, $NR^{13}R^{14}$, OR^{12}, SR^{12}, nitro, CN, halogen and -CO_2R^{12}.

Examples of hydroxy-C_1-C_6-alkyl include, for instance, hydroxymethyl, 1-hydroxyethyl and 2-hydroxyethyl. An example of halo-C_1-C_6 alkyl is trifluoromethyl. A preferred example of Ar is phenyl.

A halogen is F, Cl, Br or I. Preferably it is F, Cl or Br.

A C_3-C_{10} cycloalkyl group may be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl and is unsubstituted or substituted, for instance by one or more of the options specified above as substituents for C_1-C_6 alkyl. Typically it is C_3-C_6 cycloalkyl. A C_2-C_6 alkenylene group contains one or more unsaturated bonds. It may be, for instance, vinylene, propenylene, butenylene or pentenylene. A C_2-C_6 alkynylene group may be ethynylene, propynylene, butynylene or pentynylene.

A saturated 5-, 6-, 7- or 8-membered N-containing heterocyclic ring may be, for example, piperidine, piperazine, morpholine or pyrrolidine. When R^3 and R^4 form, together with the N and C atoms to which they are attached, a fused saturated ring as defined above the ring thereby formed is typically a saturated 5-, 6- or 7-membered ring containing one nitrogen atom and no additional heteroatoms. The ring is preferably unsubstituted. A saturated heterocyclic ring containing one nitrogen atom which contains one or two bridgehead atoms may be, for example, diazabicyclo[2,2,1]heptane.

An unsaturated C_6-C_{10} carbocyclic group is a 6-, 7-, 8-, 9- or 10-membered carbocyclic ring containing at least one unsaturated bond. It is a monocyclic or fused bicyclic ring system. The group is aromatic or non-aromatic. Examples include phenyl, naphthyl, indanyl, indenyl and tetrahydronapthyl groups.

An unsaturated 5-11-membered heterocyclic group may be, for example, furan, thiophene, pyrrole, indole, isoindole, pyrazole, imidazole, benzothiophene, benzothiazole, benzofuran, isoxazole, oxazole, oxadiazole, thiazole, isothiazole, thiadiazole, dihydroimidazole, pyridine, quinoline, isoquinoline, quinoxaline, thienopyrazine, pyran, pyrimidine, phthalimide, pyridazine, pyrazine, purine, triazine, triazole, tetrazole, chromene-4-thione, 1,3,4,5-tetramethyl-1,5-dihydro-pyrrol-2-one or uracil. In the definition of Ar this heterocyclic group is typically selected from pyridine, indole, thiophene, quinoline, isoquinoline, benziothiazole, pyrazole, benzofuran, pyrimidine, benzothiophene, pyrrole, imidazole and thiazole.

An unsaturated 5- or 6-membered heterocyclic group which contains 1, 2 or 3 heteroatoms selected from N, O and S may be selected from suitable examples of a 5- to 11-membered heterocyclic group as defined above. In the definition of R^5 this heterocyclic group is typically selected from thiazole, triazole, oxadiazole, imidazole, pyrimidine, dihydroimidazole, pyridine, pyrrole and pyrazole.

When R^5 is an unsaturated 5- or 6-membered heterocyclic group which contains 1, 2 or 3 heteroatoms selected from N, O and S and is substituted, or $NR^{10}R^{11}$ is a saturated 5- or 6-membered nitrogen-containing heterocyclic group which is fused to a substituted benzene ring, or R^9 is $-(CH_2)_nC_3$-C_{10} cycloalkyl, wherein the cycloalkyl group is fused to a substituted benzene ring, the substituted moiety in each case is typically substituted by one or more groups specified above as substituents for C_1-C_6 alkyl. Preferably the moiety is substituted by a group selected from R^{12}, OR^{12}, CO_2R^{12}, CF_3, halogen, $-NO_2$, CN, $-C(O)NR^{13}R^{14}$, $-NR^{12}C(O)R^{12}$, $-NR^{13}R^{14}$, SR^{12}, $-(CH_2)_nO(CH_2)_nAr^2$, $-O(CH_2)_nC(O)NR^{13}R^{14}$ and $-S(O)_2R^{12}$.

When R^9 is C_1-C_6 alkyl which is substituted it is typically substituted as specified above for C_1-C_6 alkyl, preferably by hydroxy-C_1-C_6 alkyl wherein the alkyl moiety is unsubstituted or substituted as specified herein for C_1-C_6 alkyl, C_1-C_6 alkoxy, Ar, $N(R^{12})_2$ wherein R^{12} is as defined below or hydroxy. When R^6 and R^7 together form a heterocyclic ring as defined above which is substituted, it is typically substituted by one or more of the groups specified above as substituents for C_1-C_6 alkyl. Preferably the ring is substituted by R^9, $-OR^9$, $-(CH_2)_nNR^{10}R^{11}$,

$-(CH_2)C(O)NR^{10}R^{11}$, $-(CH_2)_nOR^9$, $-(CH_2)_nC(O)(CH_2)_nR^9$, $-(CH_2)_nC(O)NC(O)Ar^2$ or $-(CH_2)_nO(CH_2)_nAr^2$.

When $NR^{10}R^{11}$ or $NR^{16}R^{17}$ is a heterocyclic group as defined above which is substituted, suitable substituents include the options specified above as substituents for C_1-C_6 alkyl and the groups specified below as options for Z.

Suitable substituents for an unsaturated C_6-C_{10} membered carbocyclic group or an unsaturated 5-11 membered heterocyclic group as defined above include the options specified above as substituents for C_1-C_6 alkyl. Preferably the carbocyclic or heterocyclic group is substituted by one or more groups selected from R^{12}, $-OR^{12}$, halogen, $-NO_2$, CN, $-CO_2R^{12}$, $-C(O)NR^{13}R^{14}$, CF_3, $-NR^{12}C(O)R^{12}$, $-NR^{13}R^{14}$, $-SR^{12}$, $-(CH_2)_nO(CH_2)_nAr^2$, $-O(CH_2)_nC(O)NR^{13}R^{14}$, $-S(O)_2R^{12}$, $-N(C(O)R^{12})_2$, $-S(O)_2NR^{13}R^{14}$ and $NR^{12}S(O)_2R^{12}$, or two adjacent atoms in the ring are substituted by a methylenedioxy or an ethylenedioxy group.

R^{12} is the same or different when more than one is present within a given substituent group and is selected from H, C_1-C_6 alkyl which is unsubstituted or substituted, $-(CH_2)_nC_3$-C_{10} cycloalkyl and $-(CH_2)_nAr^2$.

R^{13} and R^{14} are the same or different and are selected from H, C_1-C_6 alkyl which is unsubstituted or substituted, $-(CH_2)_nC_3$-C_{10}cycloalkyl and $-(CH_2)_nAr^2$, or R^{13} and R^{14} form, together with the nitrogen atom to which they are attached, a saturated five or six membered nitrogen containing heterocyclic ring which contains 0 or 1 additional heteroatom selected from O, S and N.

Ar^2 is an unsaturated C_6-C_{10} membered carbocyclic group or an unsaturated 5-11 membered heterocyclic group, either of which is unsubstituted or substituted by one or more groups selected from C_1-C_6 alkyl, OZ, halogen, nitro, -CN, $-CO_2Z$, $C(O)NR^{16}R^{17}$, CF_3, $NZC(O)Z$, $-N(C(O)Z)_2$ $-NR^{16}R^{17}$, -SZ, $O(CH_2)_nC(O)NR^{16}R^{17}$, $S(O)_2Z$, $-S(O)_2NR^{16}R^{17}$ and $NZS(O)_2Z$, or two adjacent atoms are substituted by a methylenedioxy or ethylenedioxy group.

Z is the same or different when more than one is present within a given substituent group and is selected from H, C_1-C_6 alkyl which is unsubstituted or substituted and C_3-C_{10} cycloalkyl;

R^{16} and R^{17} are the same or different and are selected from H, C_1-C_6 alkyl which is unsubstituted or substituted and $-(CH_2)_nC_3$-C_{10} cycloalkyl, or R^{16} and R^{17} form, together with the nitrogen atom to which they are attached, a saturated 5 or 6 membered nitrogen-containing heterocyclic group which contains 0, 1 or 2 additional heteroatoms selected from O, S and N and which is unsubstituted or substituted by Z.

Examples of preferred compounds of the invention are:

Compound Number	Chemical Name
1	4-(4-Phenyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
2	4-(4-Methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
3	4-(4-Pyrimidin-2-yl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
4	4-[4-(2-Hydroxy-ethyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
5	4-(4-Benzyl-piperazin-1-yl)-6,7,8,9-tetrahydro-5H-1,3,4b-triaza-benzo[a]azulene-10-carbonitrile
6	4-(4-Phenethyl-piperazine-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
7	2-(9-Cyano-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-ylamino)-N,N-diethyl-4-methoxy-benzenesulfonamide
8	4-(4-Phenethyl-piperazin-1-yl)-5H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile
9	1-[4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-9-yl]-ethanone
10	Cyclopentyl-[4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-9-yl]-methanone
11	4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbothioic acid amide
12	9-(4-Methyl-thiazol-2-yl)-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene
13	4-Piperazin-1-yl-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
14	4-[4-(3-Phenyl-propyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
15	4-(4-Phenylacetyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
16	5-Methyl-4-(4-phenethyl-piperazin-1-yl)-5H-pyrrolo[3,2,d]pyrimidine-7-carbonitrile
17	3-Methyl-1-[4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-9-yl]-butan-1-one
18	4-{4-[2-(1H-Indol-3-yl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
19	4-(4-Diphenylacetyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-

	carbonitrile
20	4-[4-(2-Oxo-2-phenyl-ethyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
21	4-(4-Phenylmethanesulfonyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
22	4-(4-Phenethyl-piperazin-1-yl)-9-(4-phenyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene
23	9-(4-tert-Butyl-thiazol-2-yl)-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene
24	5-Ethyl-4-(4-phenethyl-piperazin-1-yl)-5H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile
25	4-(4-Phenethyl-piperazin-1-yl)-9-(4-trifluoromethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene
26	9-(4,5-Dimethyl-thiazol-2-yl)-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene
27	5-Phenethyl-4-(4-phenethyl-piperazin-1-yl)-5H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile
28	2-[4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-9-yl]-thiazole-4-carboxylic acid; hydrobromide
29	[4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-9-yl]-phenyl-methanone
30	4-{4-[2-(4-Nitro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
31	4-{4-[2-(4-Methoxy-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
32	4-[4-(2-Cyclohexyl-ethyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
33	4-(4-Phenethyl-piperazin-1-yl)-9-thiazol-2-yl-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene
34	4-[4-(2-Naphthalen-1-yl-ethyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
35	4-(3-Methyl-4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
36	4-{4-[2-(3-Trifluoromethyl-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
37	4-{4-[2-(3-Chloro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
38	4-{4-[2-(3-Nitro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
39	4-[4-(2-o-Tolyl-ethyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
40	4-{4-[2-(2-Fluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
41	4-[4-(2-Piperidin-1-yl-ethyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

42	4-{4-[2-(4-Hydroxy-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
43	9-Ethynyl-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene
44	5,6-Dimethyl-4-(4-phenethyl-piperazin-1-yl)-5H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile
45	4-[4-(2-Phenyl-propyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
46	[4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-9-yl]-methanol
47	4-(4-Phenethyl-piperazin-1-yl)-9-piperidin-1-ylmethyl-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene
48	4-{4-[2-(4-Cyano-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
49	2-Iodo-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
50	N-Hydroxy-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxamidine
51	2-[4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-9-yl]-thiazole-4-carboxylic acid ethyl ester
52	4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid amide
53	6-Benzyl-4-{4-[2-(3,4-difluoro-phenyl)-ethyl]-piperazin-1-yl}-5-methyl-5H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile
54	4-(4-Indan-2-yl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
55	4-(4-Phenethyl-piperazin-1-yl)-2-phenyl-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
56	4-{2-[4-(9-Cyano-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl)-piperazin-1-yl]-ethyl}-benzoic acid; hydrochloride
57	4-{4-[2-(3,4,5-Trimethoxy-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
58	9-(5-Methyl-1H-[1,2,4]triazol-3-yl)-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene
59	4-{4-[2-(3-Amino-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
60	3-(2-{4-[9-(4,5-Dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl]-piperazin-1-yl}-ethyl)-benzoic acid methyl ester
61	9-(4,5-Dimethyl-thiazol-2-yl)-4-{4-[2-(3-nitro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene
62	2-(3-Methoxy-phenyl)-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
63	2-(4-Nitro-phenyl)-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
64	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-

	triaza-fluorene-9-carbonitrile
65	4-{4-[2-(3,5-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
66	4-{4-[2-(2,3-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
67	4-{4-[2-(2,4-Dichloro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
68	2-(4-Amino-phenyl)-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
69	N-{4-[9-Cyano-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-2-yl]-phenyl}-acetamide
70	N-{4-[9-Cyano-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-2-yl]-phenyl}-benzamide
71	N-{4-[9-Cyano-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-2-yl]-phenyl}-isonicotinamide
72	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-9-(4,5-dihydro-1H-imidazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene
73	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-6-isopropyl-5-methyl-5H-pyrrolo[3,2-d]pyrimidine-7-carboxylic acid amide
74	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-9-(4,5-dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene
75	N-(3-{2-[4-(9-Cyano-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl)-piperazin-1-yl]-ethyl}-phenyl)-acetamide
76	N-(3-{2-[4-(9-Cyano-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl)-piperazin-1-yl]-ethyl}-phenyl)-methane sulfonamide
77	9-(5-Methyl-thiazol-2-yl)-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene
78	9-(5-Methyl-[1,2,4]oxadiazol-3-yl)-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene
79	9-(4,5-Dimethyl-thiazol-2-yl)-4-[4-(2-pyridin-4-yl-ethyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene
80	4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid ethylamide
81	4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbothioic acid ethylamide
82	4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid benzylamide
83	4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (pyridin-3-ylmethyl)-amide
84	4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid cyclohexylmethyl-amide
85	9-(4,5-Dimethyl-1H-imidazol-2-yl)-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene
86	Bis-Hydrochloride salt of 4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-2-pyridin-4-yl-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

87	1-[4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-9-yl]-ethanone O-methyl-oxime
88	1-[4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-9-yl]-ethanone O-benzyl-oxime
89	4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxamidine dihydrochloride salt
90	4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid 2-methyl-benzylamide
91	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-2-pyridin-3-yl-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
92	9-(4,5-Dimethyl-thiazol-2-yl)-4-(4-naphthalen-2-yl methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene
93	9-(4,5-Dimethyl-thiazol-2-yl)-4-(4-quinolin-2-ylmethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene
94	4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid 2-chloro-benzylamide
95	9-(4,5-Dimethyl-thiazol-2-yl)-4-[4-(2-thiophen-2-yl-ethyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene
96	4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid 2-methoxy-benzylamide
97	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5-methyl-6-phenyl-5H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile
98	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-3(S)-methyl-piperazin-1-yl}-5,6,7,8 -tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
99	4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid methyl ester
100	4-(9-Cyano-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl)-piperazine-1-carboxylic acid phenylamide
101	9-(4,5-Dimethyl-thiazol-2-yl)-4-[4-(1-methyl-1H-indol-3-ylmethyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene
102	4-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-ylmethyl)-piperazin-1-yl]-9-(4,5-dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene
103	3-(2-{4-[9-(4,5-Dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl]-piperazin-1-yl}-ethyl)-N,N-dimethyl-benzamide
104	4-(9-Cyano-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl)-piperazine-1-carboxylic acid ethylamide
105	4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid 2,3-dimethoxy-benzylamide
106	3-(2-{4-[9-(4,5-Dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl]-piperazin-1-yl}-ethyl)-benzamide
107	9-(4,5-Dimethyl-thiazol-2-yl)-4-(4-quinolin-4-ylmethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene
108	4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid 3-cyano-benzylamide
109	4-(4-Benzo[b]thiophen-3-ylmethyl-piperazin-1-yl)-9-(4,5-dimethyl-thiazol-2-yl)-

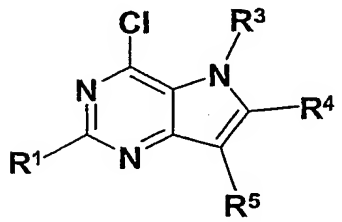
	5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene
110	4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (pyridin-2-ylmethyl)-amide
111	9-(4,5-Dimethyl-thiazol-2-yl)-4-[4-(1H-indol-3-ylmethyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene
112	4-({[4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonyl]-amino}-methyl)-benzoic acid methyl ester
113	4-(4-Benzofuran-2-ylmethyl-piperazin-1-yl)-9-(4,5-dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene
114	4-(4-Benzo[1,3]dioxol-5-ylmethyl-piperazin-1-yl)-9-(4,5-dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene
115	9-(4,5-Dimethyl-thiazol-2-yl)-4-[4-(1H-indol-5-ylmethyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene
116	3-(2-{4-[9-(4,5-Dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl]-piperazin-1-yl}-ethyl)-N-methyl-benzamide
117	4-(4-Biphenyl-4-ylmethyl-piperazin-1-yl)-9-(4,5-dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene
118	1-{4-[9-(4,5-Dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl]-piperazin-1-yl}-3-(quinolin-5-yloxy)-propan-2-ol
119	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid amide
120	9-(4,5-Dimethyl-thiazol-2-yl)-4-{4-[2-(4-methylsulfanyl-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene
121	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid 2,3-dimethoxy-benzylamide
122	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid 4-methoxy-benzylamide
123	9-(4,5-Dimethyl-thiazol-2-yl)-4-{4-[2-(4-nitro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene; hydrochloride
124	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-2-o-tolyl-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
125	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-9-pyrimidin-2-yl-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene
126	9-(4,5-Dimethyl-thiazol-2-yl)-4-[4-(3-phenoxy-benzyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene
127	9-(4,5-Dimethyl-thiazol-2-yl)-4-(4-{2-[4-(pyrrolidine-1-sulfonyl)-phenyl]-ethyl}-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene
128	4-(4-Phenoxymethyl-piperidin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
129	9-(4,5-Dimethyl-thiazol-2-yl)-4-[4-(3-phenyl-prop-2-ynyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene
130	2-{4-[9-(4,5-Dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl]-piperazin-1-yl}-1-morpholin-4-yl-ethanone
131	9-(4,5-Dimethyl-thiazol-2-yl)-4-(4-pentyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

132	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid
133	2-{4-[9-(4,5-Dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl]-piperazin-1-yl}-acetamide
134	2-{4-[9-(4,5-Dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl]-piperazin-1-yl}-N-isopropyl-acetamide
135	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-6-ethyl-5-methyl-5H-pyrrolo[3,2-d]pyrimidine-7-carboxylic acid amide
136	2-(4-{4-[9-(4,5-Dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl]-piperazin-1-ylmethyl}-phenoxy)-N,N-dimethyl-acetamide
137	9-(4,5-Dimethyl-thiazol-2-yl)-4-[4-(5-pyridin-2-yl-thiophen-2-ylmethyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene
138	4-(4-Benzothiazol-2-ylmethyl-piperazin-1-yl)-9-(4,5-dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene
139	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (6-methyl-pyridin-3-yl)-amide
140	9-(4,5-Dimethyl-thiazol-2-yl)-4-(4-quinolin-3-ylmethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene
141	2-{4-[9-(4,5-Dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl]-piperazin-1-yl}-N-(3,4,5-trimethoxy-phenyl)-acetamide
142	2-{4-[9-(4,5-Dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl]-piperazin-1-yl}-N-(3-nitro-phenyl)-acetamide
143	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (pyridin-3-ylmethyl)-amide
144	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid phenethyl-amide
145	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (pyridin-2-ylmethyl)-amide
146	2-{4-[9-(4,5-Dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl]-piperazin-1-yl}-N-(1H-pyrazol-3-yl)-acetamide
147	2-(4-{4-[9-(4,5-Dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl]-piperazin-1-ylmethyl}-phenoxy)-1-morpholin-4-yl-ethanone
148	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid 4-dimethylamino-benzylamide
149	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid 2-pyrrolidin-1-yl-benzylamide
150	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (2,2-dimethyl-propyl)-amide
151	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid 2-morpholin-4-yl-benzylamide
152	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid 2,4-dimethoxy-benzylamide
153	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid 2-(4-methyl-piperazin-1-yl)-benzylamide
154	4-[4-(6,7-Difluoro-quinolin-2-ylmethyl)-piperazin-1-yl]-9-(4,5-dimethyl-thiazol-

	2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene
155	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (benzo[1,3]dioxol-4-ylmethyl)-amide
156	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid isobutyl-amide
157	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (quinolin-2-ylmethyl)-amide
158	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (quinolin-4-ylmethyl)-amide
159	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (3-nitro-phenyl)-amide
160	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid 2,6-dimethoxy-benzylamide
161	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (3-methoxy-phenyl)-amide
162	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid pyridin-3-ylamide
163	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid phenylamide
164	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid pyridin-2-ylamide
165	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid pyridin-4-ylamide
166	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (3-dimethylamino-phenyl)-amide
167	4-(4-Phenethyl-piperazin-1-yl)-9-pyrimidin-2-yl-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene
168	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid ethylamide
169	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6-dimethyl-5H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile
170	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-6,7,8,9-tetrahydro-5H-1,3,4b-triaza-benzo[a]azulene-10-carbonitrile
171	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-6,7,8,9-tetrahydro-5H-1,3,4b-triaza-benzo[a]azulene-10-carboxylic acid amide
172	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6-dimethyl-5H-pyrrolo[3,2-d]pyrimidine-7-carboxylic acid amide
173	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-2,3-dihydro-1H-3a,5,7-triaza-cyclopenta[a]indene-8-carboxylic acid amide
174	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid propylamide
175	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (4-methyl-pyridin-3-yl)-amide
176	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid pyrimidin-5-ylamide

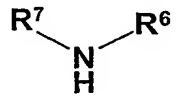
177	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (5-bromo-pyridin-3-yl)-amide
178	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide
179	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (6-methoxy-pyridin-3-yl)-amide
180	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid isoquinolin-4-ylamide
181	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid quinolin-3-ylamide
182	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (5-pyrrolidin-1-yl-pyridin-3-yl)-amide
183	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide
184	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (6-methyl-pyridin-2-ylmethyl)-amide
185	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-2,3-dihydro-1H-3a,5,7-triaza-cyclopenta[a]indene-8-carboxylic acid ethylamide
186	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-6,7,8,9-tetrahydro-5H-1,3,4b-triaza-benzo[a]azulene-10-carboxylic acid ethylamide
187	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-6-isopropyl-5-methyl-5H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile
188	4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-6-ethyl-5-methyl-5H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile
189	4-Morpholin-4-yl-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
190	4-Pyrrolidin-1-yl-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
191	4-(Methyl-phenethyl-amino)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
192	4-(4-Hydroxy-4-phenyl-piperidin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
193	4-[(3-Dimethylamino-propyl)-methyl-amino]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
194	4-[(2-Cyano-ethyl)-methyl-amino]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile
195	4-[(9-Cyano-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl)-methyl-amino]-butyric acid
196	1-(9-Cyano-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl)-piperidine-4-carboxylic acid phenylamide
197	4-[4-(Benzyl-methyl-amino)-piperidin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

Compounds of Formula (I) may be prepared by a process which comprises treating a compound of Formula (II)



II

wherein R^1, R^3, R^4 and R^5 are as defined above for formula (I), with a compound of formula (III)



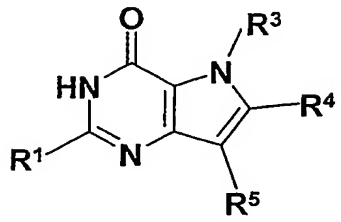
III

wherein R^6 and R^7 are as defined above, in an organic solvent in the presence of a base. The solvent is typically an aprotic solvent, for example N,N-dimethylformamide or acetonitrile. Alternatively it is a protic solvent, typically an alcohol, for example isopropanol. The reaction is typically conducted with warming. The reaction may for example be carried out at the reflux temperature of the solvent. The preferred temperature range for the reaction is 80-150°C. The base may be an organic amine, typically a tertiary amine, for example triethylamine. Alternatively the base may be an inorganic carbonate, typically an alkali metal or alkaline earth metal carbonate, for example potassium carbonate.

Compounds of formula III are either commercially available or are prepared using standard chemistry and are described in the reference examples which follow.

If desired one compound of formula (II) may be converted into another compound of formula (II) by conventional methods. For example, a compound of formula (II) with a hydrogen atom in position R^1 may be converted into a compound of formula (II) with a trialkyl tin group in position R^1 by treatment with a base and a trialkyl tin halide.

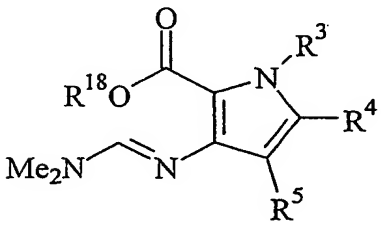
A compound of formula (II) may be prepared from a compound of formula (IV)



IV

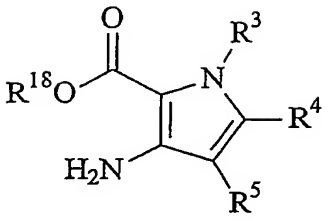
wherein R^1, R^3, R^4 and R^5 are as defined above, by treatment with a chlorinating agent. Suitable chlorinating agents include phosphorous oxychloride, thionyl chloride and sulphuryl chloride. The preferred chlorinating agent is phosphorous oxychloride. The reaction is generally conducted with warming. The reaction may for example be carried out at the reflux temperature of the solvent. The preferred temperature range for the reaction is 80-150°C. This route is particularly preferred for compounds of formula (IV) where R^1 is H. A substituent R1 may be introduced at a later stage, for instance during transformations to compounds of formula (II)

A compound of formula (IV) may be prepared from a compound of formula (V)



(V)

wherein R^{18} is a C_1-C_6 alkyl group and R^3, R^4 and R^5 are as defined above, by treatment with ammonia in an organic solvent. The reaction is typically conducted with warming. The reaction may for example be carried out at the reflux temperature of the solvent. The preferred temperature is 60-200°C. The solvent is preferably a protic solvent, typically an alcohol, for example ethanol. A compound of formula (V) may be prepared from a compound of formula VI



(VI)

wherein R^{18}, R^3, R^4 and R^5 are as defined above, by treatment with N,N-dimethylformamide dimethyl acetal in an organic solvent. The solvent is preferably an aprotic solvent, for example N,N-dimethylformamide. The reaction is typically conducted with warming. The reaction may for example be carried out at the reflux temperature of the solvent. The preferred temperature range for the reaction is 80-150°C.

Compounds of formula (VI) are prepared using standard chemistry and are described in the reference examples which follow.

The scheme used to prepare compounds of formula (II) is described in the literature (Kadushkin, A.V. et al Pharm. Chem. J. (Engl. Transl.), 24,12,1990, pp875-881; Khim. Farm. Zh. 24, 12, 1990, 18-22, and related references)

If desired one compound of formula (I) may be converted into another compound of formula (I) by conventional methods.

For example, a compound of the invention containing a nitrile group may be converted into a compound of the invention containing either an acid group or a primary amide group by acid or alkali hydrolysis. Alternatively a compound of the invention containing a nitrile group may be converted into a compound of the invention containing a primary amide group by treatment with hydrogen peroxide and sodium hydroxide.

A compound of the invention containing a nitrile group may be converted into a compound of the invention containing an aldehyde group by treatment with aluminium/nickel and formic acid.

A compound of the invention containing an aldehyde group may be converted into a compound of the invention containing an imidazole group by treatment with a 1,2-dione and ammonium acetate.

A compound of the invention containing an aldehyde group may be converted into a compound of the invention containing an acetylene group by treatment with trimethysilyl diazomethane.

A compound of the invention containing an aldehyde group may be converted into a compound of the invention containing an amine group by reductive amination.

A compound of the invention containing a primary or secondary amine group may be converted into a compound of the invention containing an amide, sulphonamide or urea group by treatment with an acyl chloride, a sulphonyl chloride or an isocyanate respectively.

A compound of the invention containing a carboxylic acid may be converted into a compound of the invention containing an ester group using standard esterification conditions.

A compound of the invention containing a secondary amine group may be converted into a compound of the invention containing a tertiary amine group by treatment with an alkyl halide in the presence of base, or alternatively by using reductive amination conditions with the appropriate carbonyl containing compound.

A compound of the invention containing an aldehyde group may be converted into a compound of the invention containing a hydroxy methyl group by reduction, for instance by using sodium borohydride.

A compound of the invention containing a primary amide group may be converted into a compound of the invention containing a secondary amide group by treatment with an aldehyde in the presence of triethylsilane and trifluoroacetic acid. (Tet. Lett. 40 (1999), pp2295-2298)

A compound of the invention containing a primary amide group may be converted into a compound of the invention containing a secondary amide group by treatment with an aryl halide using a palladium catalyst (Org Lett 2000 pp1101-1104)

A compound of the invention containing a nitrile group may be converted into a compound of the invention containing a ketone group by treatment with a Grignard reagent.

A compound of the invention containing a nitrile group may be converted into a compound of the invention containing a thioamide group by treatment with sodium hydrosulphide.

A compound of the invention containing a thioamide group, for instance a primary thioamide, group may be converted into a compound of the invention containing a thiazole group, which may be optionally substituted, by treatment with an α-haloketone or an α-haloaldehyde.

A compound of the invention containing a thioamide group, for instance a primary thioamide, group may be converted into a compound of the invention containing a triazole group by treatment with acetic hydrazide.

A compound of the invention containing a trialkyl tin group may be converted into a compound of the invention containing an aryl group by treatment with an aryl halide in the presence of a palladium catalyst.

A compound of the invention containing an alkyl ketone group may be converted into a compound of the invention containing an oxime group by treatment with the appropriately substituted hydroxylamine.

A compound of the invention containing a benzyl group may be converted into a compound of the invention in which the benzyl group has been removed, by hydrogenolysis.

A compound of the invention containing an acidic NH group may be alkylated by treatment with an appropriate base, such as sodium hydride, and addition of the appropriate alkylating agent, for instance an alkyl halide.

A compound of the invention containing a nitro group may be converted into a compound of the invention containing a primary amine group by reduction.

A compound of the invention containing a carboxylic acid group may be converted into a compound of the invention containing an amide group by treatment with an amine and a coupling reagent such as 1,1-carbonyldiimidazole.

A compound of the invention containing a nitrile group may be converted into a compound of the invention containing an amidoxime group by treatment with hydroxylamine.

A compound of the invention containing an amidoxime group may be converted into a compound of the invention containing an oxadiazole group, which may be optionally substituted, by treatment with an acyl chloride.

A compound of the invention containing an amidoxime group may be converted into a compound of the invention containing an amidine group by treatment with palladium on carbon.

A compound of the invention containing a amidine group may be converted into a compound of the invention containing a pyrimidine group, by treatment with malonaldehyde bis(dimethylacetal)

A compound of the invention containing a primary amide group may be converted into a compound of the invention containing an ester group by treatment with acetyl chloride and an alcohol.

A compound of the invention containing a nitrile group may be converted into a compound of the invention containing a dihydroimidazole group by treatment with a 1,2-diamine and phosphorous pentasulphide.

Pyrrolopyrimidines of formula (I), (Ia) or (Ib) may be converted into pharmaceutically acceptable salts, and salts may be converted into the free compound, by conventional methods. . Pharmaceutically acceptable salts include salts of inorganic acids such as hydrochloric acid, hydrobromic acid and sulfuric acid, and salts of organic acids such as acetic acid, oxalic acid, malic acid, methanesulfonic acid, trifluoroacetic acid, benzoic acid, citric acid and tartaric acid. In the case of compounds of the invention bearing a free carboxy substituent, the salts include both the above-mentioned acid addition salts and the salts of sodium, potassium, calcium and ammonium. The latter are prepared by treating the free pyrrolopyrimidine of formula 1, or the acid addition salt thereof, with the corresponding metal base or ammonia.

Cancer cells which exhibit multi-drug resistance, referred to as MDR cells, display a reduction in intracellular drug accumulation compared with the

corresponding drug-sensitive cells. Multidrug resistance is conferred by two different integral membrane proteins, the 170kDa P-glycoprotein (Pgp) and the 190kDa multidrug resistance protein (MRP). MDR is often associated with increased expression of the plasma membrane glycoprotein (P-gp) which has drug binding properties. P-gp is thought to function as an efflux pump for many hydrophobic compounds, and transfection studies using cloned P-gp have shown that its overexpression can confer the MDR phenotype on cells: see, for example, Ann. Rev. Biochem 58 137-171 (1989).

MRP is widely distributed in normal tissues including peripheral blood, endocrine glands (adrenal and thyroid), striated muscle, lymphoreticular tissues (spleen and tonsil), tissues from the digestive tract (salivary gland, oesophagus, liver, gall bladder, pancreas and colon), respiratory tract (lung) and urogenital tract (kidney, bladder, testis, and ovary).

ABC transporters such as MRP play an essential role in defending against toxic compounds. MRP1 gene knockout mice (-/-) are hypersensitive to etoposide (Wijnholds J, Evers R, van Leusden MR, Mol CAAM, Zaman GJR, Mayer U, Beijnen JH, van der Valk M, Krimpenfort P, Borst P (1997) Increased sensitivity to anticancer drugs and decreased inflammatory response in mice lacking MRP. Nat. Med. *11*: 1275-1279) and this is especially seen in bone marrow, testis, kidney, the oropharyngeal mucosa – cells with a substantial MRP content (Wijnholds J, Scheffer M, van der Valk M, Beijnen JH, Scheper RJ, Borst P (1998) MRP protects the oropharyngeal mucosal layer and the testicular tubules against drug induced damage. J. Exp. Med. *188*: 797-808).

Some insight into the normal physiological role of MRP has also been obtained by the demonstration that membrane vesicles from MRP-overexpressing drug-selected and transfected cells support ATP-dependent transport of the cysteinyl leukotriene, LTC_4 (Loe DW, Almquist KC, Deeley RG, Cole SPC. (1996) MRP-mediated transport of LTC_4 and chemotherapeutic agents in membrane vesicles. *J Biol Chem* 271 9675-9682). The cysteinyl leukotrienes (LTC_4, LTD4 and LTE4) are potent mediators of inflammation that increase vascular permeability and smooth muscle contraction. LTC_4 is derived from arachidonic acid in a series of reactions

that result in conjugation of glutathione and LTA_4 by LTC_4 synthase. It is then exported from the cell by MRP. LTC_4 is actively transported across the plasma membrane by MRP, and extracellularly LTD4 and LTE4 are formed by the action of γ- glutamyl transpeptidase and dipeptidase, respectively (Leier J, Jedlitschky G, Buchholz U, Cole SP, Deeley RG, Keppler D (1994). The MRP gene encodes an ATP-dependent export pump for Leukotriene C_4 and structurally related conjugates. J. Biol. Chem. *269*: 27807-27810). LTC_4 synthase and MRP are both expressed in eosinophils and mast cells; these cell types play a pivotal role in asthma by IgE-mediated synthesis and release of cysteinyl leukotrienes.

Inhibition of MRP-mediated transport is being targeted as a mechanism for reversing resistance to cytotoxic drugs in different cancers (a multidrug resistance modulator). Inhibition of LTC_4 transport by MRP may prevent associated inflammation and bronchoconstriction, for example in asthma (LTC_4 efflux inhibitor).

The human MRP family has at least nine members, including MRP1, MRP2 and MRP3. MRPs are organic anion transporters, meaning that they transport anionic drugs (such as methotrexate) and neutral drugs conjugated to acidic ligands (such as glutathione, glucuronate and sulphate). Drugs, such as anticancer drugs, may also be transported alongside free glutathione.

The ubiquitous nature of MRP1 in normal human tissues implies that it is potentially also present in most tumours. In fact, MRP1 protein or mRNA has been detected in most types of tumour examined including solid tumours and haematological malignancies.

Compounds of the invention have been found in biological tests to have activity as inhibitors of MRP. Compounds of the invention have also been found to be selective for MRP over P-gp with a range of selectivity from about 20-fold to greater than 200-fold. A compound of the present invention may thus be used as an inhibitor of MRP, in particular MRP1. A compound of the present invention may also be used as an LTC_4 efflux inhibitor. The present compounds can be used to modulate MDR, in particular MRP-mediated MDR. The present compounds may thus be used as multi-drug resistance modifying agents, also termed resistance-

modifying agents, or RMAs. The present compounds can modulate, e.g. reduce, or eliminate multi-drug resistance, especially that which is MRP mediated.

The present compounds can be used in a method of potentiating the cytotoxicity of a chemotherapeutic agent. Such a method comprises, for instance, administering one of the present compounds to the tumour cell whilst the tumour cell is exposed to the chemotherapeutic agent in question. The therapeutic effect of a chemotherapeutic, or antineoplastic, agent may thus be enhanced. The multi-drug resistance of a tumour cell to a chemotherapeutic agent during chemotherapy may be reduced or eliminated.

The present compounds can also be used in a method of treating a disease in which the responsible pathogen exhibits multi-drug resistance, especially MRP-mediated MDR multi-drug resistance, for instance multi-drug resistant forms of malaria (*Plasmodium falciparum*), tuberculosis, leishmaniasis and amoebic dysentery. Such a method comprises, for instance, administering one of the present compounds with (separately, simultaneously or sequentially) the drug to which the pathogen concerned exhibits multi-drug resistance. The therapeutic effect of a drug directed against a multidrug resistant pathogen may thus be potentiated.

Leukotrienes, such as LTC_4, are also considered important for antibacterial defence. In the lung it has been shown that mice lacking MRP1 are resistant to pneumonia (J. Immunol. 2001, pp 4059-64; Schultz MJ *et al*). These results suggest that inhibition of MRP1 may have benefit in therapy for diseases such as pneumonia. According, one of the present compounds may be used to treat a bacterial infection, for instance pneumonia.

Inhibition of MRP may also be of benefit in the management of epilepsy. In a recent study MRP1 was found to be over-expressed in human brain tissue containing focal cortical dysplasia, the most common malformation causing refractory epilepsy (The Lancet 2001, vol 357 no. 9249, p. 42 Sisodiya *et al*). Over-expression of MRP1 could have a major effect on the drug responsiveness in epilepsy and inhibition of MRP1 in refractory epilepsy may offer an alternative treatment strategy. Accordingly, one of the present compounds may be used to treat a patient suffering from epilepsy.

A human or animal patient harbouring a tumour may be treated for resistance to a chemotherapeutic agent by a method comprising the administration thereto of one of the present compounds. The present compound is administered in an amount effective to potentiate the cytotoxicity of the said chemotherapeutic agent. Examples of chemotherapeutic or antineoplastic agents which are preferred in the context of the present invention include mitoxantrone; vinca alkaloids such as vincristine and vinblastine; anthracycline antibiotics such as daunorubicin and doxorubicin; alkylating agents such as chlorambucil and melphalan; taxanes such as paclitaxel; antifolates such as methotrexate and tomudex; epipodophyllotoxins such as etoposide; and camptothecins such as irinotecan and its active metabolite SN-38. There is also some evidence linking expression of MRP, in particular MRP2, with resistance to platinum-containing compounds such as cisplatin. Further, there is evidence linking expression of MRP, in particular MRP4 and MRP5, with resistance to nucleotide analogues such as 6-mercaptopurine and 6-thioguanine.

The present compounds may also be used in a method of enhancing the absorption, distribution, metabolism and/or elimination characteristics of a therapeutic agent, which method comprises administering to a patient, separately, simultaneously or sequentially, one of the present compounds and the said therapeutic agent. In particular this method may be used to enhance the penetration of the therapeutic agent into the central nervous system, or to enhance the oral absorption of the therapeutic agent. For instance, the present compounds can be used in a method of facilitating the delivery of drugs across the blood brain barrier, and in the treatment of AIDS or AIDS related complex. A human or animal patient in need of such treatment may be treated by a method comprising the administration thereto of one of the present compounds.

The present compounds may also be used in a method of treating a multidrug resistant tumour, especially a tumour in which the multidrug resistance is MRP mediated. Examples of such tumours include solid tumours, for instance lung, gastrointestinal and urothelial carcinomas, neuroblastoma, glioma, retinoblastoma, melanoma, cancers of the breast, endometrium, ovary, prostate and thyroid, and

haematological malignancies. The condition of a patient harbouring a tumour may thus be ameliorated by the administration thereto of one of the present compounds.

The present compounds can also be used in a method of treating inflammation or bronchoconstriction, for instance asthma. Also, the present compounds may be used to treat HIV infection. HIV protease inhibitor drugs, for instance ritonavir and saquinavir, are substrates for MRP. Elevated levels of MRP at sites of viral replication can reduce the accumulation of HIV inhibitors, resulting in lower intracellular drug concentrations. The inhibition of MRP by compounds of the invention can thus overcome this problem.

The present compounds can be administered in a variety of dosage forms, for example orally such as in the form of tablets, capsules, sugar- or film-coated tablets, liquid solutions or suspensions or parenterally, for example intramuscularly, intravenously or subcutaneously. The present compounds may therefore be given by injection or infusion.

The dosage depends on a variety of factors including the age, weight and condition of the patient and the route of administration. Typically, however, the dosage adopted for each route of administration when a compound of the invention is administered alone to adult humans is 0.001 to 500 mg/kg, most commonly in the range of 0.01 to 100 mg/kg, body weight, for instance 0.01 to 50 mg/kg. Such a dosage may be given, for example, from 1 to 5 times daily by bolus infusion, infusion over several hours and/or repeated administration.

A pyrrolopyrimidine of formula (I) or a pharmaceutically acceptable salt thereof is formulated for use as a pharmaceutical or veterinary composition also comprising a pharmaceutically or veterinarily acceptable carrier or diluent. The compositions are typically prepared following conventional methods and are administered in a pharmaceutically or veterinarily suitable form. An agent for use as a modulator of multi-drug resistance comprising any one of the present compounds is therefore provided.

The present compounds may be administered in any conventional form, for instance as follows:

A) Orally, for example, as tablets, coated tablets, dragees, troches, lozenges, aqueous or oily suspensions, liquid solutions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavouring agents, colouring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations.

Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, dextrose, saccharose, cellulose, corn starch, potato starch, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, maize starch, alginic acid, alginates or sodium starch glycolate; binding agents, for example starch, gelatin or acacia; lubricating agents, for example silica, magnesium or calcium stearate, stearic acid or talc; effervescing mixtures; dyestuffs, sweeteners, wetting agents such as lecithin, polysorbates or lauryl sulphate. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. Such preparations may be manufactured in a known manner, for example by means of mixing, granulating, tableting, sugar coating or film coating processes.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is present as such, or mixed with water or an oil medium, for example, peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose,

hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone gum tragacanth and gum acacia; dispersing or wetting agents may be naturally-occurring phosphatides, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides for example polyoxyethylene sorbitan monooleate.

The said aqueous suspensions may also contain one or more preservatives, for example, ethyl or n-propyl p-hydroxybenzoate, one or more colouring agents, such as sucrose or saccharin.

Oily suspension may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol.

Sweetening agents, such as those set forth above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by this addition of an antioxidant such as ascorbic acid. Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oils, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally occuring phosphatides, for example soy bean

lecithin, and esters or partial esters derived from fatty acids an hexitol anhydrides, for example sorbitan mono-oleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavouring agents. Syrups and elixirs may be formulated with sweetening agents, for example glycerol, sorbitol or sucrose. In particular a syrup for diabetic patients can contain as carriers only products, for example sorbitol, which do not metabolise to glucose or which only metabolise a very small amount to glucose.

Such formulations may also contain a demulcent, a preservative and flavouring and coloring agents;

B) Parenterally, either subcutaneously, or intravenously, or intramuscularly, or intrasternally, or by infusion techniques, in the form of sterile injectable aqueous or oleaginous suspensions. This suspension may be formulated according to the known art using those suitable dispersing of wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic paternally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol.

Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition fatty acids such as oleic acid find use in the preparation of injectables;

C) By inhalation, in the form of aerosols or solutions for nebulizers;

D) Rectally, in the form of suppositories prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperature but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and poly-ethylene glycols;

E) Topically, in the form of creams, ointments, jellies, collyriums, solutions or suspensions.

Daily dosages can vary within wide limits and will be adjusted to the individual requirements in each particular case. In general, for administration to adults, an appropriate daily dosage is in the range of about 5 mg to about 500 mg, although he upper limit may be exceeded if expedient. The daily dosage can be administered as a single dosage or in divided dosages.

The following examples illustrate the invention.

Reference Example 1: Preparation of Compounds of General Formula (VI)

Reference Example 1A:

2-Amino-1-cyano-5,6,7,8-tetrahydro-indolizine-3-carboxylic acid ethyl ester

To a 1 litre flask was added trimethyloxonium tetrafluoroborate (41.30g), delta-valerolactam (27.7g) and dry dichloromethane (330mL). The mixture was stirred for 16 hours at room temperature. The reaction mixture was then diluted with dichloromethane, washed with aqueous potassium carbonate solution, dried ($MgSO_4$) and the solvent removed in vacuo to yield 6-methoxy-2,3,4,5-tetrahydro-pyridine (31.5g)

To a solution of malonitrile (17.57mL) in ethanol was added 6-methoxy-2,3,4,5-tetrahydro-pyridine (31.5g) at room temperature. The reaction mixture was stirred overnight, filtered, yielding 2-piperidin-2-ylidene-malononitrile as a white solid (29.4g)

A mixture of 2-piperidin-2-ylidene-malononitrile (21.74g), ethyl bromoacetate (16.4mL) and potassium carbonate (40.91g) was heated to 100°C in dimethylformamide for 5 hours. The reaction mixture was then cooled and poured onto water. The precipitate produced was collected by filtration and air dried to yield the title compound (14.92g)

Commencing with the appropriate starting material, the following compounds of formula (VI) were prepared in an analogous manner.

2-Amino-1-cyano-6,7-dihydro-5H-pyrrolizine-3-carboxylic acid ethyl ester was prepared from 2-pyrrolidinone;

2-Amino-1-cyano-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-3-carboxylic acid ethyl ester was prepared from ε-caprolactam.

Reference Example 1B

3-Amino-1-benzyl-4-cyano-1*H*-pyrrole-2-carboxylic acid ethyl ester

Benzylamine (8.9mL) was added to solution of ethoxymethylenemalonitrile (5.0g) in ether (200mL) at 0°C. The reaction mixture was stirred for 5 hours and the volatiles were removed *in vacuo* until precipitation commenced. The resulting precipitate was collected by filtration to yield 2-(benzylamino-methylene)-malononitrile as a yellow solid (4.93g).

To a stirred solution of 2-(benzylamino-methylene)-malononitrile (5.41g) in dimethylformamide (100mL) was added ethyl bromoacetate (3.27mL) and potassium carbonate (4.08g). Reaction mixture was heated to 80°C for 30 minutes, before cooling to 50°C. Sodium ethoxide (38.3mL of a 1.0M solution) was added and the reaction mixture stirred for a further 25 minutes at 90°C. After cooling, water was added and the precipitate was collected by filtration to yield the title compound as an off-white solid (7.1g).

The following compounds of formula (VI) were prepared in an analogous manner from the appropriate starting compounds

3-Amino-4-cyano-1,5-dimethyl-1H-pyrrole-2-carboxylic acid ethyl ester was prepared by starting with methylamine and (1-ethoxyethylidene)-malononitrile.

Reference Example 1C

3-Amino-4-cyano-5-isopropyl-1-methyl-1H-pyrrole-2-carboxylic acid ethyl ester

To a solution of malonitrile (7.13g) and isobutyryl chloride (11.31mL) in dichloromethane (80mL) was added a solution of benzyl triethyl ammonium chloride (0.63g) in dichloromethane (10mL). To this was added a 10N aqueous solution of sodium hydroxide (25.3mL) with rapid stirring. After stirring overnight, the organic phase was removed. The aqueous phase was acidified (HCl, 2N), extracted into

dichloromethane, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield 2-(1-hydroxy-2-methyl-propylidene)-malononitrile (14.3g) as a viscous oil.
To 2-(1-hydroxy-2-methyl-propylidene)-malononitrile (4.7g) in diethyl ether (50mL) was added a solution of freshly prepared diazomethane (excess) in diethyl ether. After stirring for 2 hours, residual diazomethane was quenched with acetic acid, and the mixture was then reduced *in vacuo* to yield crude 2-(1-methoxy-2-methyl-propylidene)-malononitrile.
Methylamine gas was bubbled through a suspension of 2-(1-methoxy-2-methyl-propylidene)-malononitrile (5.18g, crude) in diethyl ether at 0°C. After stirring for 16 hours the reaction mixture was reduced *in vacuo* and the residue was purified using flash chromatography to yield 2-(2-methyl-1-methylamino-propylidene)-malononitrile (2.47g).
A mixture of 2-(2-methyl-1-methylamino-propylidene)-malononitrile (2.47g), ethyl bromoacetate (1.84mL) and potassium carbonate (2.2 equivalents) was heated to 100°C in dimethylformamide (30mL) for 5 hours. The reaction mixture was then cooled and poured onto water. The precipitate produced was collected by filtration and air dried to yield the title compound (1.5g)

The following compounds of formula (VI) were prepared in an analogous manner from the appropriate starting compounds
3-Amino-4-cyano-5-ethyl-1-methyl-1H-pyrrole-2-carboxylic acid ethyl ester;
3-Amino-4-cyano-1-methyl-5-phenyl-1H-pyrrole-2-carboxylic acid ethyl ester;
3-Amino-5-benzyl-4-cyano-1-methyl-1H-pyrrole-2-carboxylic acid ethyl ester.

Reference Example 2: Preparation of Compounds of General Formula (V)

Reference Example 2A:

1-Cyano-2-(dimethylamino-methyleneamino)-5,6,7,8-tetrahydro-indolizine-3-carboxylic acid ethyl ester

A mixture of 2-amino-1-cyano-5,6,7,8-tetrahydro-indolizine-3-carboxylic acid ethyl ester (14.92g), N,N-dimethylformamide dimethylacetal (17mL) and dimethylformamide (95mL) was heated at 100°C for 5 hours. The reaction mixture

was then cooled and the solvent removed *in vacuo* to yield an oil which slowly crystallised. Trituration from ether yielded the title compound as a pale solid (15.1g)

The following compounds of formula (V) were prepared in an analogous manner from the appropriate compound of formula (VI)

1-Cyano-2-(dimethylamino-methyleneamino)-6,7-dihydro-5H-pyrrolizine-3-carboxylic acid ethyl ester;
1-Cyano-2-(dimethylamino-methyleneamino)-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-3-carboxylic acid ethyl ester;
1-Benzyl-4-cyano-3-(dimethylamino-methyleneamino)-1H-pyrrole-2-carboxylic acid ethyl ester;
4-Cyano-3-(dimethylamino-methyleneamino)-1,5-dimethyl-1H-pyrrole-2-carboxylic acid ethyl ester;
4-Cyano-3-(dimethylamino-methyleneamino)-5-isopropyl-1-methyl-1H-pyrrole-2-carboxylic acid methyl ester;
4-Cyano-3-(dimethylamino-methyleneamino)-5-ethyl-1-methyl-1H-pyrrole-2-carboxylic acid methyl ester;
5-Benzyl-4-cyano-3-(dimethylamino-methyleneamino)-1-methyl-1H-pyrrole-2-carboxylic acid methyl ester;
4-Cyano-3-(dimethylamino-methyleneamino)-1-methyl-5-phenyl-1H-pyrrole-2-carboxylic acid methyl ester.

Reference Example 3: Preparation of Compounds of General Formula (IV)

Reference Example 3a.

4-oxo-3,4,5,6,7,8-hexahydro-1,3,4b-triaza-fluorene-9-carbonitrile

A saturated solution of ammonia in ethanol (270mL) was prepared at 0°C and mixed with 1-cyano-2-(dimethylamino-methyleneamino)-5,6,7,8-tetrahydro-indolizine-3-carboxylic acid ethyl ester (87.2g). The mixture was heated to 110°C in a sealed bomb overnight. The volatiles were removed *in vacuo* and the remaining solid was stirred in 10% aqueous sodium hydroxide solution for 30 minutes. Any solid

persisting was removed by filtration. The filtrate was then neutralised to pH 7 using acetic acid and the precipitated solid collected by filtration to yield the title compound (59.74g)

The following compounds of formula (IV) were prepared in analogous manner from the appropriate compound of formula (V);

4-Oxo-2,3,4,5-tetrahydro-1H-3a,5,7-triaza-cyclopenta[a]indene-8-carbonitrile;
4-Oxo-4,5,6,7,8,9-hexahydro-3H-1,3,4b-triaza-benzo[a]azulene-10-carbonitrile;
5-Benzyl-4-oxo-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile;
5,6-Dimethyl-4-oxo-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile;
6-Isopropyl-5-methyl-4-oxo-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile;
6-Ethyl-5-methyl-4-oxo-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile;
6-Benzyl-5-methyl-4-oxo-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile;
5-Methyl-4-oxo-6-phenyl-4,5-dihydro-3H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile;

Reference Example 3b Conversion of one compound of formula (IV) into another compound of formula (IV)

9-(4,5-Dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-3H-1,3,4b-triaza-fluoren-4-one

A mixture of sodium hydrosulfide (23.30g), 4-oxo-3,4,5,6,7,8-hexahydro-1,3,4b-triaza-fluorene-9-carbonitrile (8.90g) and dimethylformamide (70mL) was heated to 60°C for 5 days. The reaction mixture was then cooled, water added, and the resulting precipitate collected by filtration to yield the desired primary thioamide (7.80g)

A mixture of the thioamide (7.80g), 3-bromo-2-butanone (4.75g) and dimethylformamide (50mL) was heated to 100°C for 7 hours. The reaction mixture was then cooled, water added, and the resulting precipitate collected by filtration to yield the title compound as cream coloured solid (8.48g)

Reference Example 4: Preparation of Compounds of General Formula (III)

Reference Example 4a

1-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazine

To a solution of 3,4-difluorophenylacetic acid (24.8g) in dry tetrahydrofuran (150mL) was added borane dimethylsulphide complex (21.6mL) at 0°C. After stirring overnight, the reaction was quenched with dilute hydrochloric acid, extracted into dichloromethane, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield 2-(3,4-difluoro-phenyl)-ethanol as an oil which slowly crystallised (21.7g)

To a cold solution of 2-(3,4-difluoro-phenyl)-ethanol (21.7g) in dry dichloromethane (150mL) was added p-toluenesulfonyl chloride (28.8g) and triethylamine (23.0mL). The reaction mixture was stirred overnight, diluted with dichloromethane, washed with water, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield toluene-4-sulfonic acid 2-(3,4-difluoro-phenyl)-ethyl ester as a gum (41.1g)

A mixture of toluene-4-sulfonic acid 2-(3,4-difluoro-phenyl)-ethyl ester (41.05g), N-BOC-piperazine (24.5g) and potassium carbonate (18.1g) was heated to reflux in acetonitrile (250mL). After 16 hours at reflux the reaction mixture was reduced *in vacuo*, dissolved in dichloromethane and washed with water, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield an oil which was purified using flash chromatography to yield 4-[2-(3,4-difluoro-phenyl)-ethyl]-piperazine-1-carboxylic acid tert-butyl ester (33.3g)

A mixture of 4-[2-(3,4-difluoro-phenyl)-ethyl]-piperazine-1-carboxylic acid tert-butyl ester (10.26g) and trifluoroacetic acid (25mL) in dichloromethane (100mL) was stirred at room temperature overnight. The reaction mixture was then basified carefully with potassium carbonate, extracted into dichloromethane, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield the title compound as an oil (6.79g)

Reference Example 5:Preparation of compounds of General Formula (II)

Reference example 5A

4-Chloro-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

A mixture of 4-oxo-3,4,5,6,7,8-hexahydro-1,3,4b-triaza-fluorene-9-carbonitrile (4.00g), triethylamine hydrochloride (1.03g) and phosphorous oxychloride (35mL) was heated to reflux for 4 hours. The reaction mixture was then poured onto

ice/water and the precipitate collected by filtration and washed with water to yield the desired title compound as a beige solid (3.53g)

The following compounds of formula (II) were prepared in analogous manner from the appropriate compound of formula (IV)
4-Chloro-2,3-dihydro-1H-3a,5,7-triaza-cyclopenta[a]indene-8-carbonitrile;
4-Chloro-6,7,8,9-tetrahydro-5H-1,3,4b-triaza-benzo[a]azulene-10-carbonitrile;
5-Benzyl-4-chloro-5H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile;
4-Chloro-5,6-dimethyl-5H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile;
4-Chloro-9-(4,5-dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene;
4-Chloro-6-isopropyl-5-methyl-5H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile
4-Chloro-6-ethyl-5-methyl-5H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile
6-Benzyl-4-chloro-5-methyl-5H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile;
4-Chloro-5-methyl-6-phenyl-5H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile.

Reference example 5B: Conversion of one compound of Formula (II) into another compound of Formula (II)

4-Chloro-2-tributylstannanyl-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

nBuLi (0.69mL of a 2.5M solution) was added to a solution of 2,2,6,6-tetramethylpiperidine in THF (5mL) at -78°C. To this was added 4-chloro-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile (100mg). After stirring for 30 minutes, tributyl tin chloride (376µL) was added. After 45 minutes the reaction mixture was quenched with ammonium chloride solution. The organics were then extracted into ethyl acetate, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield an orange solid.

Example 1: Preparation of Compounds of General Formula (I)

Example 1A

4-(4-Phenethyl-piperazine-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

A mixture of 4-chloro-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile (80mg), 1-(2-phenylethyl)-piperazine (72mg) and triethylamine (1.1 equivalents) was heated in dimethylformamide (0.5mL) at 100°C for 2 hours. The reaction mixture was cooled, poured onto ice/water and the precipitated solid collected by filtration to yield the desired title compound (94mg)

The following compounds of formula (I) were prepared in an analogous manner using the appropriate compound of formula (II) and compound of formula (III);

4-(4-Pyrimidin-2-yl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared from 1-(2-pyrimidyl)piperazine;
4-(4-Benzyl-piperazin-1-yl)-6,7,8,9-tetrahydro-5H-1,3,4b-triaza-benzo[a]azulene-10-carbonitrile was prepared from 1-benzylpiperazine;
4-[4-(2-Hydroxy-ethyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared from N-(2-hydroxyethyl) piperazine;
4-(4-Methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared from 1-methylpiperazine;
4-(4-Phenyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared from 1-phenylpiperazine;
4-Piperazin-1-yl-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared from piperazine (excess used);
4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared from 1-[2-(3,4-difluoro-phenyl)-ethyl]-piperazine;
4-(4-Benzo[1,3]dioxol-5-ylmethyl-piperazin-1-yl)-9-(4,5-dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene was prepared from 1-piperonylpiperazine;
5-Benzyl-4-(4-phenethyl-piperazin-1-yl)-5H-pyrrole[3,2,-d]pyrimidine-7-carboxamide was prepared from 1-(2-phenylethyl)-piperazine ;
5,6-Dimethyl-4-(4-phenethyl-piperazin-1-yl)-5H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile was prepared from 1-(2-phenylethyl)-piperazine ;

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-9-(4,5-dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene was prepared from 1-[2-(3,4-difluoro-phenyl)-ethyl]-piperazine ;

4-(3-(S)-Methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared from (S)-(+)-2-methylpiperazine;

4-(3-(R)-Methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile as prepared from (R)-(-)-2-methylpiperazine;

9-(4,5-Dimethyl-thiazol-2-yl)-4-piperazin-1-yl-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene was prepared from piperazine;

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6-dimethyl-5H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile was prepared from 1-[2-(3,4-difluoro-phenyl)-ethyl]-piperazine;

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-6,7,8,9-tetrahydro-5H-1,3,4b-triaza-benzo[a]azulene-10-carbonitrile was prepared from 1-[2-(3,4-difluoro-phenyl)-ethyl]-piperazine;

4-Morpholin-4-yl-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared from morpholine;

4-Pyrrolidin-1-yl-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared from pyrrolidine;

4-(Methyl-phenethyl-amino)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared from N-methylphenethylamine;

4-(4-Hydroxy-4-phenyl-piperidin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared from 4-hydroxy-4-phenylpiperidine;

4-[(3-Dimethylamino-propyl)-methyl-amino]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared from N,N,N'-trimethyl-1,3-propanediamine;

4-[(2-Cyano-ethyl)-methyl-amino]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared from N-methyl-beta-alaninenitrile;

4-[(9-Cyano-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl)-methyl-amino]-butyric acid was prepared from 4-(dimethylamino)butyric acid hydrochloride;

1-(9-Cyano-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl)-piperidine-4-carboxylic acid phenylamide was prepared from piperidine-4-carboxylic acid phenylamide,

which in turn was prepared from 4-phenylcarbamoyl-piperidine-1-carboxylic acid tert-butyl ester, which in turn was prepared by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride coupling of aniline with BOC-isonipecotic acid;
4-[4-(Benzyl-methyl-amino)-piperidin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared from benzyl-methyl-piperidin-4-yl-amine, which in turn was prepared from 4-(benzyl-methyl-amino)-piperidine-1-carboxylic acid tert-butyl ester, which in turn was prepared by a reductive amination reaction between tert-butyl 4-oxo-1-piperidinecarboxylate and N-methylbenzylamine;
4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5-methyl-6-phenyl-5H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile was prepared from 1-[2-(3,4-difluoro-phenyl)-ethyl]-piperazine;
4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-6-ethyl-5-methyl-5H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile was prepared from 1-[2-(3,4-difluoro-phenyl)-ethyl]-piperazine;
4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-6-isopropyl-5-methyl-5H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile was prepared from 1-[2-(3,4-difluoro-phenyl)-ethyl]-piperazine;
6-Benzyl-4-{4-[2-(3,4-difluoro-phenyl)-ethyl]-piperazin-1-yl}-5-methyl-5H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile was prepared from 1-[2-(3,4-difluoro-phenyl)-ethyl]-piperazine;

Example 2: Conversion of one compound of Formula (I) into another compound of Formula (I)

Example 2A

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid amide and 4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid

A solution of KOH (465mg) in water (2mL) was added to a suspension of 4-{4-[2-(3,4-difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile (500mg) in ethanol (6mL). The reaction mixture was stirred for 6 hours at reflux and then cooled. The precipitate was collected by filtration and

washed with ethanol to yield the title compound (primary amide) as a white solid (179mg).

The filtrate was neutralised, extracted into dichloromethane, and reduced *in vacuo*. Flash chromatography of this material yielded the corresponding acid, 4-{4-[2-(3,4-difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid, as a cream solid (130mg)

4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid amide was prepared in an analogous fashion from 4-(4-phenethyl-piperazine-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile.

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-2,3-dihydro-1H-3a,5,7-triaza-cyclopenta[a]indene-8-carboxylic acid amide was prepared in analogous manner from the corresponding nitrile;

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6-dimethyl-5H-pyrrolo[3,2-d]pyrimidine-7-carboxylic acid amide was prepared in analogous manner from the corresponding nitrile;

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-6,7,8,9-tetrahydro-5H-1,3,4b-triaza-benzo[a]azulene-10-carboxylic acid amide was prepared in analogous manner from the corresponding nitrile;

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-6-ethyl-5-methyl-5H-pyrrolo[3,2-d]pyrimidine-7-carboxylic acid amide was prepared in analogous manner from the corresponding nitrile;

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-6-isopropyl-5-methyl-5H-pyrrolo[3,2-d]pyrimidine-7-carboxylic acid amide was prepared in analogous manner from the corresponding nitrile;

Alternatively this reaction may be performed using hydrogen peroxide and sodium hydroxide in aqueous methanol.

Example 2B

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid 2,3-dimethoxy-benzylamide

Reference method: Tet. Lett. 40 (1999), pp2295-2298

To 4-{4-[2-(3,4-difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid amide (62mg) in acetonitrile (1.5mL) was added 2,3-dimethoxybenzaldehyde (70mg), triethylsilane (75μL) and trifluoroacetic acid (51μL). The reaction mixture was heated to reflux for 18 hours. The solvent was then removed *in vacuo* and the residue was dissolved in ethyl acetate, washed with sodium bicarbonate solution, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield crude product. This was recrystallised from dichloromethane/hexane to yield the desired title compound (76mg)

The following compounds of formula (I) were prepared in an analogous manner using the appropriate primary amide and the appropriate aldehyde;

4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid ethylamide was prepared using acetaldehyde;

4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid benzylamide was prepared using benzaldehyde;

4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (pyridin-3-ylmethyl)-amide was prepared using 3-pyridinecarboxaldehyde;

4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid cyclohexylmethyl-amide was prepared using cyclohexanecarboxaldehyde;

4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid 2-methyl-benzylamide was prepared using o-tolualdehyde;

4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid 2-chloro-benzylamide was prepared using 2-chlorobenzaldehyde;

4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid 2-methoxy-benzylamide was prepared using o-anisaldehyde;

4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid 2,3-dimethoxy-benzylamide was prepared using 2,3-dimethoxybenzaldehyde;

4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid 3-cyano-benzylamide was prepared using 3-cyanobenzaldehyde;

4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (pyridin-2-ylmethyl)-amide was prepared using 2-pyridinecarboxaldehyde;

4-({[4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonyl]-amino}-methyl)-benzoic acid methyl ester was prepared using methyl 4-formylbenzoate;

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid 4-methoxy-benzylamide was prepared using p-anisaldehyde;

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (pyridin-3-ylmethyl)-amide was prepared using 3-pyridinecarboxaldehyde;

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid phenethyl-amide was prepared using phenylacetaldehyde;

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (pyridin-2-ylmethyl)-amide was prepared using 2-pyridinecarboxaldehyde;

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid 4-dimethylamino-benzylamide was prepared using p-dimethylaminobenzaldehyde;

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid 2-pyrrolidin-1-yl-benzylamide was prepared from 2-(pyrrolidino)benzaldehyde which in turn was prepared from 2-fluorobenzaldehyde and pyrrolidine;

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (2,2-dimethyl-propyl)-amide was prepared from trimethylacetaldehyde;

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid 2-morpholin-4-yl-benzylamide was prepared from 2-morpholinobenzaldehyde;

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid 2,4-dimethoxy-benzylamide was prepared using 2,4-dimethoxybenzaldehyde;

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid 2-(4-methyl-piperazin-1-yl)-benzylamide was prepared from 2-(4-methylpiperazino)benzaldehyde;

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (benzo[1,3]dioxol-4-ylmethyl)-amide was prepared using 2,3-(methylenedioxy)benzaldehyde;

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid isobutyl-amide was prepared using isobutyraldehyde;

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (quinolin-2-ylmethyl)-amide was prepared using 2-quinolinecarboxaldehyde;

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (quinolin-4-ylmethyl)-amide was prepared using 4-quinolinecarboxaldehyde;

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid 2,6-dimethoxy-benzylamide was prepared using 2,6-dimethoxybenzaldehyde;

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid propylamide was prepared using propionaldehyde;

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide was prepared using 6-methoxy-pyridine-3-carbaldehyde (J.Org. Chem 1990,pp69-73)
4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide was prepared using 6-methyl-pyridine-3-carbaldehyde. 6-Methyl-pyridine-3-carbaldehyde was prepared by reducing methyl 6-methyl nicotinate to the corresponding alcohol using lithium aluminium hydride, and then oxidising the alcohol to the desired aldehyde using manganese dioxide;
4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (6-methyl-pyridin-2-ylmethyl)-amide was prepared from 6-methyl-2-pyridinecarboxaldehyde;
4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid ethylamide was prepared using acetaldehyde;
4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-2,3-dihydro-1H-3a,5,7-triaza-cyclopenta[a]indene-8-carboxylic acid ethylamide was prepared using acetaldehyde;
4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-6,7,8,9-tetrahydro-5H-1,3,4b-triaza-benzo[a]azulene-10-carboxylic acid ethylamide was prepared using acetaldehyde;

This reaction could also be applied to the preparation of secondary thioamides. Hence
4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbothioic acid ethylamide was prepared from reaction of acetaldehyde and the appropriate thioamide.

Example 2C

2-{4-[9-(4,5-Dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl]-piperazin-1-yl}-1-morpholin-4-yl-ethanone

4-Chloroacetyl-morpholine was prepared from morpholine and chloroacetyl chloride using Schotten-Baumann conditions.

A mixture of 9-(4,5-dimethyl-thiazol-2-yl)-4-piperazin-1-yl-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene (102mg), 4-chloroacetyl-morpholine (45mg) and potassium carbonate (46mg) in dimethylformamide (1mL) was stirred at room temperature. After 2 hours the reaction mixture was diluted with ethyl acetate, washed with brine, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield a gum, which was purified using flash chromatography (dichloromethane) to yield the title compound (58mg)

The following compounds of formula (I) were prepared in an analogous manner using the appropriate amine and the appropriate alkylating agent
4-[4-(2-Oxo-2-phenyl-ethyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared from 2-bromoacetophenone;
2-{4-[9-(4,5-Dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl]-piperazin-1-yl}-N-(3,4,5-trimethoxy-phenyl)-acetamide was prepared from chloro-acetic acid-(3,4,5-trimethoxy-anilide). Chloro-acetic acid-(3,4,5-trimethoxy-anilide) was prepared from 3,4,5-trimethoxyaniline and chloroacetyl chloride in dichloromethane using triethylamine as base.
2-{4-[9-(4,5-Dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl]-piperazin-1-yl}-N-(3-nitro-phenyl)-acetamide was prepared from chloro-acetic acid-(3-nitro-anilide). Chloro-acetic acid-(3-nitro-anilide) was prepared from 3-nitroaniline and chloroacetyl chloride in dichloromethane using triethylamine as base.
2-{4-[9-(4,5-Dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl]-piperazin-1-yl}-acetamide was prepared from 2-chloroacetamide;
2-{4-[9-(4,5-Dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl]-piperazin-1-yl}-N-isopropyl-acetamide was prepared from 2-chloro-N-isopropyl-acetamide. 2-Chloro-N-isopropyl-acetamide was prepared from isopropylamine and chloroacetyl chloride using Schotten-Baumann conditions;
2-{4-[9-(4,5-Dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl]-piperazin-1-yl}-N-(1H-pyrazol-3-yl)-acetamide was prepared from 2-chloro-N-(1H-pyrazol-3-yl)-acetamide. 2-Chloro-N-(1H-pyrazol-3-yl)-acetamide was prepared by

treating 3-aminopyrazole with chloroacetyl chloride in dichloromethane with triethylamine.

Example 2D

9-(4,5-Dimethyl-thiazol-2-yl)-4-[4-(2-thiophen-2-yl-ethyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

To a solution of 2-(2-thienyl)ethanol (1.63g) in dry ether(15mL) at 0°C was added PBr_3 (1.31mL) dropwise. After 4 hours the reaction mixture was diluted with dichloromethane, washed with water, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield a brown oil which was purified using flash chromatography to yield 2-(2-bromo-ethyl)-thiophene.

A mixture of 9-(4,5-dimethyl-thiazol-2-yl)-4-piperazin-1-yl-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene (85mg), 2-(2-bromo-ethyl)-thiophene (44mg) and potassium carbonate (38mg) was heated to reflux in acetonitrile (5mL)for 4 hours. The reaction mixture was cooled, extracted into dichloromethane, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield crude product which was purified using flash chromatography to yield the title compound (30mg).

The following compounds of formula (I) were prepared in an analogous manner using the appropriate amine and the appropriate alkylating agent. Dimethylformamide was used as the solvent for some of these reactions

4-[4-(3-Phenyl-propyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared from 1-bromo-3-phenylpropane;

4-{4-[2-(1H-Indol-3-yl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared from 3-(2-bromoethyl)indole;

4-{4-[2-(4-Nitro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared from 4-nitrophenethyl bromide;

4-{4-[2-(4-Methoxy-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared from 4-methoxyphenethyl bromide;

4-[4-(2-Cyclohexyl-ethyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared from 2-cyclohexylethyl bromide;

4-[4-(2-Naphthalen-1-yl-ethyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared from 1-bromo-2(1-naphthyl)ethane which, in turn, was prepared from the corresponding alcohol;

4-[4-(2-o-Tolyl-ethyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared from 2-methylphenethyl bromide;

4-{4-[2-(2-Fluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared from 2-fluorophenethyl bromide;

4-{4-[2-(3-Trifluoromethyl-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared from 3-(trifluoromethyl)phenethyl bromide which, in turn, was prepared from the corresponding alcohol;

4-{4-[2-(3-Chloro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared from 3-chlorophenethyl bromide which, in turn, was prepared from the corresponding alcohol;

4-{4-[2-(3-Nitro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared from 3-nitrophenethyl bromide which, in turn, was prepared from the corresponding alcohol;

4-{4-[2-(4-Hydroxy-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared from 4-hydroxyphenethyl bromide which, in turn, was prepared from the corresponding alcohol;

4-[4-(2-Phenyl-propyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared from 1-bromo-2-phenylpropane;

4-{4-[2-(4-Cyano-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared from 4-(2-bromoethyl)benzonitrile, which in turn was prepared from 4-(2-hydroxyethyl)benzonitrile;

4-{2-[4-(9-Cyano-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl)-piperazin-1-yl]-ethyl}-benzoic acid methyl ester was prepared from 4-(2-bromoethyl)-benzoic acid methyl ester, which in turn was prepared from 4-(2-bromoethyl)-benzoic acid using standard esterification conditions. This compound was converted to the corresponding carboxylic acid by treatment of the ester with lithium hydroxide in dioxane to yield 4-{2-[4-(9-cyano-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl)-

piperazin-1-yl]-ethyl}-benzoic acid; hydrochloride which was isolated as the hydrochloride salt;

3-(2-{4-[9-(4,5-Dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl]-piperazin-1-yl}-ethyl)-benzoic acid methyl ester was prepared from 4-(2-bromoethyl)-benzoic acid methyl ester;

4-{4-[2-(3,4,5-Trimethoxy-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared from 5-(2-bromo-ethyl)-1,2,3-trimethoxy-benzene, which in turn was prepared from the corresponding alcohol using PBr_3 as described above. This was prepared from 3,4,5-trimethoxyphenylacetic acid using lithium aluminium hydride.

4-{4-[2-(2,4-Dichloro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared from 2,4-dichlorophenethyl bromide which, in turn, was prepared from the corresponding alcohol;

4-{4-[2-(2,3-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared from 2,3-difluorophenethyl bromide, which in turn was prepared from the corresponding alcohol using PBr_3. This, in turn, was prepared from 2,3-difluorophenylacetic acid using borane dimethyl sulphide complex;

4-{4-[2-(3,5-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared from 3,5-difluorophenethyl bromide, which in turn was prepared from the corresponding alcohol using PBr_3. This, in turn, was prepared from 3,5-difluorophenylacetic acid using borane dimethyl sulphide complex;

4-[4-(2-Piperidin-1-yl-ethyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared from 1-(2-chloroethyl)piperidine hydrochloride;

4-(3-Methyl-4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared from phenethyl bromide;

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-3(S)-methyl-piperazin-1-yl}-5,6,7,8 -tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared from 4-(2-bromo-ethyl)-1,2-difluoro-benzene which was prepared from the corresponding alcohol;

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-9-(4,5-dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene was prepared from 4-(2-bromo-ethyl)-1,2-difluoro-benzene;

9-(4,5-Dimethyl-thiazol-2-yl)-4-{4-[2-(4-nitro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene was prepared from 4-nitrophenethyl bromide;

9-(4,5-Dimethyl-thiazol-2-yl)-4-[4-(2-pyridin-4-yl-ethyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene was prepared using 4-vinylpyridine in dimethylformamide at 100°C for 3 hours.

Example 2E

9-(4,5-Dimethyl-thiazol-2-yl)-4-(4-quinolin-2-ylmethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

A mixture of 9-(4,5-dimethyl-thiazol-2-yl)-4-piperazin-1-yl-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene (78mg), 2-quinolinecarboxaldehyde (34mg) and acetic acid (12μL) was mixed in 1,2,-dichloroethane (5mL). To this was added sodium triacetoxyborohydride (58mg) and the reaction mixture was stirred at room temperature overnight. The reaction mixture was then extracted into dichloromethane, washed with sodium carbonate solution, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield crude product. This material was recrystallised from ethyl acetate/hexane to yield the title compound (17mg).

The following compounds of formula (I) were prepared in an analogous manner using the appropriate amine and the appropriate aldehyde or ketone.

4-(4-Indan-2-yl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared from 2-indanone;

9-(4,5-Dimethyl-thiazol-2-yl)-4-(4-quinolin-4-ylmethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene was prepared from 4-quinolinecarboxaldehyde;

4-(4-Benzo[b]thiophen-3-ylmethyl-piperazin-1-yl)-9-(4,5-dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene was prepared from thianaphthene-3-carboxaldehyde;

9-(4,5-Dimethyl-thiazol-2-yl)-4-[4-(1H-indol-3-ylmethyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene was prepared from indole-3-carboxaldehyde ;

9-(4,5-Dimethyl-thiazol-2-yl)-4-[4-(1H-indol-5-ylmethyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene was prepared from indole-5-carboxaldehyde ;

9-(4,5-Dimethyl-thiazol-2-yl)-4-[4-(3-phenoxy-benzyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene was prepared from 3-phenoxybenzaldehyde;

9-(4,5-Dimethyl-thiazol-2-yl)-4-(4-quinolin-3-ylmethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene was prepared from 3-quinoline-carboxaldehyde;

4-(4-Benzothiazol-2-ylmethyl-piperazin-1-yl)-9-(4,5-dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene was prepared from 2-benzothiazolecarboxaldehyde;

9-(4,5-Dimethyl-thiazol-2-yl)-4-[4-(5-pyridin-2-yl-thiophen-2-ylmethyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene was prepared from 5-pyridin-2-ylthiophene-2-carboxaldehyde;

4-(4-Benzofuran-2-ylmethyl-piperazin-1-yl)-9-(4,5-dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene was prepared from 2-benzofurancarboxaldehyde;

9-(4,5-Dimethyl-thiazol-2-yl)-4-[4-(3-phenyl-prop-2-ynyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene was prepared from phenylpropargyl aldehyde;

9-(4,5-Dimethyl-thiazol-2-yl)-4-(4-naphthalen-2-yl methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene was prepared from 2-naphthaldehyde;

9-(4,5-Dimethyl-thiazol-2-yl)-4-[4-(1-methyl-1H-indol-3-ylmethyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene was prepared from 1-methylindole-3-carboxaldehyde;

4-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-ylmethyl)-piperazin-1-yl]-9-(4,5-dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene was prepared from 1,4-benzodioxane-6-carboxaldehyde;

9-(4,5-Dimethyl-thiazol-2-yl)-4-(4-pentyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene was prepared from valeraldehyde;

4-(4-Biphenyl-4-ylmethyl-piperazin-1-yl)-9-(4,5-dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene was prepared from 4-biphenylcarboxaldehyde;

9-(4,5-Dimethyl-thiazol-2-yl)-4-{4-[2-(4-methylsulfanyl-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene was prepared from (4-methylsulfanyl-phenyl)-acetaldehyde. This aldehyde was prepared from reaction of 4-methylthiobenzaldehyde with (methoxymethyl)triphenyl phosphonium chloride, followed by treatment with formic acid;

2-(4-{4-[9-(4,5-Dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl]-piperazin-1-ylmethyl}-phenoxy)-N,N-dimethyl-acetamide was prepared from 2-(4-formyl-phenoxy)-N,N-dimethyl-acetamide. 2-(4-Formyl-phenoxy)-N,N-dimethyl-acetamide was prepared from 4-formylphenoxyacetic acid and dimethylamine hydrochloride using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride as the coupling reagent;

2-(4-{4-[9-(4,5-Dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl]-piperazin-1-ylmethyl}-phenoxy)-1-morpholin-4-yl-ethanone was prepared from 4-(2-morpholin-4-yl-2-oxo-ethoxy)-benzaldehyde. 4-(2-Morpholin-4-yl-2-oxo-ethoxy)-benzaldehyde was prepared from 4-formylphenoxyacetic acid and morpholine using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride as the coupling reagent;

9-(4,5-Dimethyl-thiazol-2-yl)-4-(4-{2-[4-(pyrrolidine-1-sulfonyl)-phenyl]-ethyl}-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene was prepared from [4-(pyrrolidine-1-sulfonyl)-phenyl]-acetaldehyde. [4-(Pyrrolidine-1-sulfonyl)-phenyl]-acetaldehyde was prepared by diisobutylaluminium hydride reduction of the corresponding ester, [4-(pyrrolidine-1-sulfonyl)-phenyl]-acetic acid ethyl ester. [4-(Pyrrolidine-1-sulfonyl)-phenyl]-acetic acid ethyl ester was prepared by reaction of pyrrolidine with (4-chlorosulfonyl-phenyl)-acetic acid ethyl ester. (4-Chlorosulfonyl-phenyl)-acetic acid ethyl ester was prepared by reaction of ethyl phenyl acetate with chlorosulphonic acid in 1,2-dichloroethane;

4-[4-(6,7-Difluoro-quinolin-2-ylmethyl)-piperazin-1-yl]-9-(4,5-dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene was prepared from 6,7-difluoro-quinoline-2-carbaldehyde, which in turn was prepared by selenium dioxide mediated

oxidation of 6,7-diflouro-2-methylquinoline (Tetrahedron Asymmetry 997, pp161-168)

Example 2F

4-(4-Phenethyl-piperazin-1-yl)-9-piperidin-1-ylmethyl-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

A mixture of 4-(4-Phenethyl-piperazine-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile (1.95g), aluminium/nickel (3.38g), formic acid (29mL) and water (29mL) was heated to 80°C for 7 hours. The reaction mixture was then cooled, basified (sodium carbonate), extracted into chloroform, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield the crude desired aldehyde as an off-white foam (2.4g).

A mixture of the aldehyde (150mg) and piperidine (46µL) was stirred in methanol (4mL) and dichloromethane (0.5mL) for 10 minutes over 3Å molecular sieves. Sodium cyanoborohydride (72mg) was then added. After stirring overnight the reaction mixture was quenched with water, extracted into chloroform, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield a gum which was purified using column chromatography to yield the desired title compound (28mg)

[4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-9-yl]-methanol was also isolated form this reaction as a by-product

Example 2G

Cyclopentyl-[4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-9-yl]-methanone

To a solution of cyclopentyl magnesium bromide (2.0M solution in ether, 0.58mL) and dry tetrahydrofuran (0.5mL) was added a solution of 4-(4-phenethyl-piperazine-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile (150mg) dropwise. The reaction mixture was heated to 60°C for 4 hours. The reaction mixture was then cooled, quenched with water, extracted into ethyl acetate, dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified using flash chromatography to yield the title compound as a white solid (55mg).

The following compounds of formula (I) were prepared in an analogous manner using the appropriate nitrile and the appropriate Grignard reagent.
1-[4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-9-yl]-ethanone was prepared from methyl magnesium bromide;
3-Methyl-1-[4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-9-yl]-butan-1-one was prepared from isobutyl magnesium bromide;
[4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-9-yl]-phenyl-methanone was prepared from phenylmagnesium bromide;

Example 2H

4-(4-Phenylacetyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

To a suspension of 4-piperazin-1-yl-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile (100mg) and triethylamine (60μL) in dichloromethane (3mL) was added phenyl acetyl chloride (47 μL). After 10 minutes the reaction mixture was diluted with dichloromethane, washed with water, dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified using flash chromatography to yield the title compound as a white solid (80mg).
The following compounds of formula (I) were prepared in an analogous manner using the appropriate amine and the appropriate acid chloride, sulphonyl chloride or isocyanate
4-(4-Diphenylacetyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared from diphenylacetyl chloride;
4-(4-Phenylmethanesulfonyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared from α-toluene sulphonyl chloride;
4-(9-Cyano-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl)-piperazine-1-carboxylic acid phenylamide was prepared from phenyl isocyanate in refluxing acetonitrile;
4-(9-Cyano-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl)-piperazine-1-carboxylic acid ethylamide was prepared from ethyl isocyanate in refluxing acetonitrile;

Example 2I

9-Ethynyl-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

To dry tetrahydrofuran was added trimethylsilyl-diazomethane (2.0M solution, 520μL) at -78°C. To this was added lithium bis(trimethylsilyl)amide (1.0M solution in THF, 1.04mL) and the mixture was stirred for 10 minutes. To this was added a solution of the aldehyde (prepared in Example 2F above)(162mg) in dry THF (2mL). The reaction mixture was warmed to room temperature over 3 hours, and then quenched with water, extracted into ethyl acetate, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield a gum. Purification using column chromatography yielded the title compound (10mg)

Example 2J

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-2-pyridin-3-yl-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

4-Chloro-2-tributylstannanyl-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile (see Ref Example 5B) and 1-[2-(3,4-difluoro-phenyl)-ethyl]-piperazine were reacted together to yield 4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-2-tributylstannanyl-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile.

A mixture of 4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-2-tributylstannanyl-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile (360mg), 3-iodopyridine(106mg), toluene (3.7mL), $Pd(PPh_3)_4$ (7.7mg) and copper iodide (19.4mg) was heated to reflux for 1 day. The reaction mixture was then cooled, diluted with ethyl acetate, washed with sodium bicarbonate solution, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield crude product which was purified using flash chromatography to yield the title compound (8mg)

The following compounds of formula (I) were prepared in an analogous manner from the appropriate tin derivative with the appropriate reagent.

2-(3-Methoxy-phenyl)-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared using 3-iodoanisole;

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-2-pyridin-4-yl-5,6,7,8-

tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared using 4-iodopyridine;
2-(4-Nitro-phenyl)-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared using 1-iodo-4-nitrobenzene;
4-(4-Phenethyl-piperazin-1-yl)-2-phenyl-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared using iodobenzene;
2-Iodo-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared using iodine;
4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-2-o-tolyl-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared using 2-iodotoluene;

Example 2K

4-(4-Phenethyl-piperazin-1-yl)-5H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile

A mixture of 5-Benzyl-4-(4-phenethyl-piperazin-1-yl)-5H-pyrrole[3,2,-d]pyrimidine-7-carboxamide (1.41g), ethanol (20mL), cyclohexene (12mL), and palladium black (20mg) was heated to reflux for 9 hours. After cooling the reaction mixture was filtered through celite, reduced *in vacuo* and then purified using flash chromatography to yield the title compound (572mg)

Example 2L

5-Methyl-4-(4-phenethyl-piperazin-1-yl)-5H-pyrrolo[3,2,d]pyrimidine-7-carbonitrile

To a cold solution of 4-(4-phenethyl-piperazin-1-yl)-5H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile (18mg) in dimethylformamide (1mL) was added sodium hydride (60% suspension in mineral oil, 2.25mg). After stirring for 20 minutes, methyl iodide (5μL) was added. After 30 minutes, the reaction mixture was quenched with water, extracted into ethyl acetate, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield crude product which was purified using flash chromatography to yield the title compound.

The following compounds of formula (I) were prepared in an analogous manner from the appropriate compound of formula (I) and the appropriate alkylating agent;
5-Ethyl-4-(4-phenethyl-piperazin-1-yl)-5H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile was prepared from ethyl iodide;
5-Phenethyl-4-(4-phenethyl-piperazin-1-yl)-5H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile was prepared from phenethyl bromide;

Example 2M

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid pyridin-3-ylamide

Reference Procedure: Org Lett 2000 pp1101-1104

A mixture of 4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid amide (100mg) and 3-bromopyridine (1.1. equivalents) was stirred in 1,4-dioxane (1.5mL). To this was added caesium carbonate (111mg), tris(dibenzylideneacetone)dipalladium (2mg) and Xanthphos (2mg). The reaction mixture was heated to 100°C overnight. After cooling, the reaction mixture was extracted into dichloromethane, washed with water, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield crude product which was purified using flash chromatography to yield the title compound.

The following compounds of formula (I) were prepared in an analogous manner from the appropriate primary amide and the appropriate aryl halide;
4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (3-nitro-phenyl)-amide was prepared from 1-bromo-3-nitrobenzene;
4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (3-dimethylamino-phenyl)-amide was prepared from 3-bromo-N,N, dimethylaniline;
4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (3-methoxy-phenyl)-amide was prepared from 3-bromoanisole;

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid phenylamide was prepared from bromobenzene;

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid pyridin-2-ylamide was prepared from 2-bromopyridine;

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid pyridin-4-ylamide was prepared from 4-bromopyridine;

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (4-methyl-pyridin-3-yl)-amide was prepared from 3-bromo-4-methylpyridine;

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid pyrimidin-5-ylamide was prepared from 5-bromopyrimidine;

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (5-bromo-pyridin-3-yl)-amide was prepared from 3,5-dibromopyridine;

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (6-methoxy-pyridin-3-yl)-amide was prepared from 5-bromo-2-methoxy-pyridine;

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid isoquinolin-4-ylamide was prepared from 4-bromoisoquinoline;

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid quinolin-3-ylamide was prepared from 3-bromoquinoline;

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (5-pyrrolidin-1-yl-pyridin-3-yl)-amide was prepared from 3-bromo-5-pyrrolidin-1-yl-pyridine, which in turn was prepared by reaction of pyrrolidine with 3,5-dibromopyridine in dimethylformamide;
4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (6-methyl-pyridin-3-yl)-amide was prepared from 3-bromo-6-methylpyridine (J.Med.Chem 1987, pp871-880)

Example 2N

4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbothioic acid amide

To a solution of 4-(4-Phenethyl-piperazine-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile (3.3g) in dimethylformamide (30mL) was added sodium hydrosulphide hydrate (4.7g). The reaction mixture was heated at 60°C for 5 days. After cooling, the reaction mixture was extracted into ethyl acetate, washed with water, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield crude product which was purified using flash chromatography to yield the title compound (2.20g)

Example 2O

9-(4-Methyl-thiazol-2-yl)-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

A mixture of 4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbothioic acid amide (600mg), triethylamine (0.3mL) and chloroacetone (0.15mL) was heated to 100°C for 2.5 hours. The volatiles were then removed *in vacuo*, and the reside triturated with water and filtered to yield a beige coloured solid, which was purified using flash chromatography to yield the title compound as a white solid (485mg)

The following compounds of formula (I) were prepared in an analogous manner by using the appropriate primary thioamide and the appropriate α-haloketone or α-haloaldehyde;

9-(5-Methyl-thiazol-2-yl)-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene was prepared using 2-bromopropionaldehyde;
4-(4-Phenethyl-piperazin-1-yl)-9-(4-phenyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene was prepared using 2-bromoacetophenone;
9-(4-tert-Butyl-thiazol-2-yl)-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene was prepared using 1-bromopinacolone;
4-(4-Phenethyl-piperazin-1-yl)-9-(4-trifluoromethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene was prepared using 1-bromo-3,3,3-trifluoroacetone;
2-[4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-9-yl]-thiazole-4-carboxylic acid; hydrobromide was prepared using 3-bromopyruvic acid hydrate and isolated as the hydrobromide salt;
2-[4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-9-yl]-thiazole-4-carboxylic acid; hydrobromide was converted into the corresponding ester using standard esterification conditions.
4-(4-Phenethyl-piperazin-1-yl)-9-thiazol-2-yl-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene was prepared using chloroacetaldehyde (in water);
9-(4,5-Dimethyl-thiazol-2-yl)-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene was prepared using 3-bromo-2-butanone;

Example 2P

4-(4-Phenethyl-piperazin-1-yl)-9-pyrimidin-2-yl-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

A mixture of 4-(4-Phenethyl-piperazine-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile (725mg), potassium carbonate (1.04g) and hydroxylamine hydrochloride (457mg) in ethanol (16mL) was heated to reflux overnight. The reaction mixture was reduced *in vacuo*, triturated with water and a precipitate collected. This was triturated with hot dichloromethane to yield the desired amidoxime (430mg)
To N-Hydroxy-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxamidine (430mg) in acetic acid (5mL) was added acetic anhydride (154μL) and the mixture stirred for 10 minutes. Palladium (10%) on carbon was then

added (110mg) and the mixture stirred under a positive pressure of hydrogen for 5 hours. The reaction mixture was then filtered through celite, and the volatiles were removed *in vacuo*. The residue was dissolved in dichloromethane, washed with sodium bicarbonate solution, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield the desired amidine. This was converted into the dihydrochloride salt by treatment with HCl in methanol.

To 4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxamidine dihydrochloride salt (105mg) in Dowtherm (2mL) was added potassium carbonate (30.4mg) and malonaldehyde bis(dimethylacetal)(120μL) . Reaction mixture was heated to 175°C for 5 hours. The reaction mixture was cooled, diluted with ethyl acetate, extracted into 2M HCL, neutralised ($NaHCO_3$), extracted into dichloromethane, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield crude product which was purified using flash chromatography to yield the title compound (80mg)

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-9-pyrimidin-2-yl-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene was prepared in a similar manner from the corresponding nitrile.

Example 2Q

1-[4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-9-yl]-ethanone O-methyl-oxime

A mixture of 1-[4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-9-yl]-ethanone (see Example 2G above) methoxylamine hydrochloride (50mg) and potassium acetate (70mg) was stirred in ethanol (1.5mL) at room temperature overnight. The reaction mixture was extracted into dichloromethane, washed with sodium bicarbonate solution, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield crude product which was purified by recrystallisation from ethyl acetate to yield the desired compound as a white solid (34mg)

In a similar manner 1-[4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-9-yl]-ethanone O-benzyl-oxime was prepared using O-benzylhydroxylamine.

Example 2R

9-(4,5-Dimethyl-1H-imidazol-2-yl)-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

To the aldehyde (prepared in Example 2F above)(380mg) in acetic acid (4mL) was added ammonium acetate (550mg) and 2,3-butanedione (170mg), and heated at 60°C for 24 hours. The reaction mixture was cooled, extracted into dichloromethane, washed with sodium bicarbonate solution, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield crude product which was purified by flash chromatography to yield the title compound as a beige solid (42mg)

Example 2S

9-(5-Methyl-[1,2,4]oxadiazol-3-yl)-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

A mixture of the amidoxime (prepared in Example 2P above)(188mg) and acetyl chloride (48μL) in pyridine (1.5mL) was heated to 60°C for 6 hours. The reaction mixture was cooled, extracted into dichloromethane, washed with sodium bicarbonate solution, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield crude product which was purified by flash chromatography to yield the title compound as a beige solid (37mg)

Example 2T

9-(5-Methyl-1H-[1,2,4]triazol-3-yl)-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

A mixture of the primary thioamide (prepared in Example 2N above)(250mg) and acetic hydrazide (1.5g) in m-xylene (3mL) was heated to reflux for 4 days. The reaction mixture was cooled, extracted into dichloromethane, washed with sodium bicarbonate solution, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield crude

product which was purified by flash chromatography to yield the title compound (67mg)

Example 2U

4-{4-[2-(3-Amino-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

To a solution of 4-{4-[2-(3-Nitro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile (100mg) in ethanol (1mL) was added ammonium chloride solution (0.5mL) and indium powder (186mg). The mixture was heated at reflux overnight. The reaction mixture was then cooled, diluted with water and filtered through celite. The aqueous filtrate was basified using sodium hydroxide solution, extracted into dichloromethane, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield crude product which was purified by flash chromatography to yield the title compound (20mg)

In a similar manner, 2-(4-amino-phenyl)-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile was prepared from 2-(4-nitro-phenyl)-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile (described in Example 2J)

Example 2V

N-(3-{2-[4-(9-Cyano-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl)-piperazin-1-yl]-ethyl}-phenyl)-acetamide

To a stirring solution of 4-{4-[2-(3-amino-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile (150mg) in dichloromethane (1mL) was added acetic anhydride (0.035mL) and triethylamine (0.052mL). After 3 hours at room temperature the reaction mixture was diluted with dichloromethane, washed with water, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield crude product which was purified by flash chromatography to yield the title compound (105mg).

In an analogous manner the following compounds of formula (I) were prepared by using the appropriate amine and the appropriate acylating or sulphonylating agent;
N-(3-{2-[4-(9-Cyano-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl)-piperazin-1-yl]-ethyl}-phenyl)-methane sulfonamide was prepared using methane sulphonyl chloride;
N-{4-[9-Cyano-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-2-yl]-phenyl}-acetamide was prepared using acetic anhydride;
N-{4-[9-Cyano-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-2-yl]-phenyl}-benzamide was prepared using benzoyl chloride;
N-{4-[9-Cyano-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-2-yl]-phenyl}-isonicotinamide was prepared using isonicotinoyl chloride;

Example 2W
3-(2-{4-[9-(4,5-Dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl]-piperazin-1-yl}-ethyl)-N,N-dimethyl-benzamide

To a solution of 3-(2-{4-[9-(4,5-Dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl]-piperazin-1-yl}-ethyl)-benzoic acid methyl ester (560mg) in 1,4-dioxane (10mL) was added a solution of lithium hydroxide (89mg) in water. After several hours the reaction was reduced *in vacuo*, and the residue dissolved in water. Hydrochloric acid was carefully added to this until precipitation occurred. The precipitate was collected by filtration and air-dried to yield the desired carboxylic acid (350mg)

To a solution of the carboxylic acid (75mg) in dimethylformamide (1mL) was added 1,1,-carbonyldiimidazole (46mg). After 4 hours, a solution of dimethylamine hydrochloride (23mg) and triethylamine (0.04mL) in dimethylformamide (0.5mL) were added. After 6 hours at room temperature the reaction mixture was diluted with ethyl acetate, washed with water, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield crude product which was purified by flash chromatography to yield the title compound (39mg).

In an analogous manner the following compounds of formula (I) were prepared by using the appropriate amine;

3-(2-{4-[9-(4,5-Dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl]-piperazin-1-yl}-ethyl)-N-methyl-benzamide was prepared using methylamine hydrochloride;

3-(2-{4-[9-(4,5-Dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl]-piperazin-1-yl}-ethyl)-benzamide was prepared using ammonium hydroxide;

Example 2X

1-{4-[9-(4,5-Dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl]-piperazin-1-yl}-3-(quinolin-5-yloxy)-propan-2-ol

5-Hydroxyquinoline (0.60g) was added to a stirring solution of potassium t-butoxide (0.55g) in dimethylformamide (12mL). The mixture was then heated to 50°C for 30 minutes. The reaction was then cooled, and epichlorohydrin (0.97mL) added. The reaction mixture was then warmed to 90°C for 3 hours. The mixture was then cooled, poured onto ice/water, extracted into ethyl acetate, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield an oil which was purified by flash chromatography to yield the desired epoxide, 5-oxiranylmethoxy-quinoline (0.54g)

A mixture of 9-(4,5-dimethyl-thiazol-2-yl)-4-piperazin-1-yl-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene (75mg) and 5-oxiranylmethoxy-quinoline (38mg) was heated in ethanol (1mL) to reflux for 5 hours. The reaction mixture was then reduced *in vacuo* and the residue purified by flash chromatography to yield the title compound (88mg)

Example 2Y

4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid methyl ester

A mixture of 4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid amide (300mg), acetyl chloride (0.75mL) and methanol (4mL) was heated to 50°C for 4 days. The solvent was then removed *in vacuo*, and the residue dissolved in dichloromethane, washed with sodium bicarbonate solution,

dried ($MgSO_4$) and the solvent removed *in vacuo* to yield a solid which was purified using flash chromatography to yield the title compound as an off white solid (20mg)

Example 2Z

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-9-(4,5-dihydro-1H-imidazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

A mixture of 4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile (300mg), phosphorous pentasulphide (47mg) and ethylenediamine (3mL) was heated to 120°C for 18 hours. The reaction mixture was then cooled, and water added to yield a precipitate which was collected by filtration to yield the desired title compound (81mg)

Example 2AA

4-(4-Phenoxymethyl-piperidin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

A mixture of 4-chloro-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile (119mg), 4-hydroxymethylpiperidine (55mg), and triethylamine (86µL) was heated in dimethylformamide (1mL) at 100°C for 2 hours. The mixture was then cooled, poured onto ice/water, extracted into ethyl acetate, dried ($MgSO_4$) and the solvent removed *in vacuo* to yield 4-(4-hydroxymethyl-piperidin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile (0.16g)

A mixture of 4-(4-hydroxymethyl-piperidin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile (89mg), phenol (35mg), diethylazodicarboxylate (59µL) and triphenylphosphine (98mg) was stirred in dry tetrahydrofuran (1mL). After 2 hours the reaction mixture was reduced *in vacuo* and the residue purified using flash chromatography to yield the title compound (13mg).

Example 3: Testing of the compounds of formula (I) as modulators of MRP

Materials and Methods

The COR.L23 human large cell lung cancer cell line and an MRP expressing drug selected multidrug resistant subline COR.L23/R were cultured at 37°C in 5% CO_2 in

RPMI 1640 medium containing 10% foetal calf serum and 2mM glutamine. Drug resistance was maintained in COR.L23 cells by intermittent culture in 100 ng/mL doxorubicin.

1. Drug Accumulation Assay

COR.L23/R were seeded 48 hours prior to assay into 96 well opaque culture plates (Canberra Packard). The assay medium contained tritiated daunomycin (0.3μCi/mL), a cytotoxic anthracycline (NEN). Compounds of formula (I) were serially diluted in assay medium over a range of concentrations from 10-5000 nM. The cells were incubated at 37°C for 2 hours, before washing and determination of cell associated radioactivity. Results are expressed as an IC_{50} for tritiated daunomycin accumulation where 100% accumulation is that observed in the presence of a standard inhibitor, 38, at a concentration of 10 μM. Compounds of Formula (I) were active in the range 20nM to 5μM.

A selection of compounds is shown in Table 1 below.

Table 1

Accumulation assay	
Compound No.	**IC_{50} (μM)**
38	**0.35 (n=60)**
6	**0.69**
14	**7.3**
64	**0.22**
111	**3.3**
119	**0.19**
121	**0.043**
162	**0.076**
168	**0.087**

2. Potentiation of Doxorubicin Cytotoxicity

Selected compounds of formula (I) were examined for their ability to potentiate the cytotoxicity of doxorubicin for COR.L23/R cells. Cells were cultured for five days with a titration of doxorubicin (0.263nM-17.24μM) in the presence of compound at a range of concentrations from 16-2000nM. Cell viability was quantified by a fluorometric method using alamarBlue, a non-toxic metabolic indicator of viable

cells that becomes fluorescent upon mitochondrial reduction (Nociari, M.M et al, J. Immunol Methods, 1998, pp157-167). The IC_{50} (concentration required to reduce viable cells to 50% of the untreated controls) for doxorubicin alone, and for doxorubicin in the presence of each compound over the concentration range, were derived and used to calculate the EC_{50}. The EC_{50} is the compound concentration effecting potentiation of doxorubicin cytotoxicity to 50% of the R_f value where

$$R_f = \frac{IC_{50} \text{ for doxorubicin, COR.L23/R cells}}{IC_{50} \text{ for doxorubicin, COR.L23 cells}}$$

Compounds of Formula (I) were active in the range 20nM to 5μM.
A selection of compounds is shown in Table 2 below.

Table 2

Compound No.	EC_{50} (μM)
38	0.31
107	0.87
119	0.12
145	0.098

For a selection of compounds of Formula (I), the potentiation assay was also performed using a different cell line and also a variety of cytotoxics using the protocol described above. The results are shown in Table 3

Table 3

Compound No.	Cell Line	Cytotoxic	EC_{50} (μM)
6	L23/R	Vincristine	0.24
38	L23/R	Etoposide	0.52
38	L23/R	Methotrexate	0.12
64	HT1080/DR4	Vincristine	0.17
145	HT1080/DR4	Vincristine	0.06

3. Demonstration of activity against MRP1 in MDCK cells

Cytotoxic drug transport (daunomycin and/or vinblastine) was measured across polarised cell monolayers of MDCK cells: parental or transfected with either MRP1

or MRP2 (Drug export activity of the human canalicular multispecific organic anion transporter in polarized kidney MDCK cells expressing cMOAT (MRP2) cDNA. R. Evers et al ,*J Clin Invest* 1998 Apr 1 101:7 1310-9). Compound **191** at 2–20 μM completely inhibited MRP1 transport.

4. Inhibition of LTC_4 transport

The effects of the compounds **26** and **119** on the function of human MRP1 and MRP2 proteins in a vesicular transport system has been studied. The assay examines the modulation of radiolabelled LTC_4 uptake in isolated MRP1 or MRP2 expressing Sf9 cell membranes (Interactions of the human multidrug resistance proteins MRP1 and MRP2 with organic anions. Bakos, E. et al, *Mol Pharmacol* 2000 Apr 57:4 760-8; Borst, P., *J Biol Chem* 1998 Nov 27 **273:48** 32167-75 and Functional multidrug resistance protein (MRP1) lacking the N-terminal transmembrane domain. Bakos, E. et al, *J Biol Chem* 1998 Nov 27, 273:48, 32167-75).

Compounds **26** and **119** acted as effective, high affinity inhibitors of LTC_4 transport by MRP1 (1.0 and 0.7μM respectively).

Example 4: Characterisation of the present compounds

The compounds prepared in the preceding Examples were characterised by proton N.M.R spectroscopy and mass spectroscopy. All proton N.M.R were performed at 300 or 400MHz. Characterisation by mass spectroscopy was performed using desorption chemical ionisation or electrospray ionisation. The results are set out in Table 4:

Table 4

Compound No.	Molecular formula	Mass spec. data	^{1}H NMR data (ppm)
1	C21H22N6	ESI+ MH+ 359	(CDCl3), 2.05 (4H, m, 2xCH2), 3.25 (2H, t, CH2), 3.40 (4h, m, 2xCH2), 3.55 (4H, m), 4.45 (2H, t), 6.90 (1H, t), 7.00 (2H, d), 7.35 (2H, m), 8.65 (1H, s).
2	C16H20N6	ESI,	(CDCl3), 2.05 (4H, m, 2xCH2), 2.40 (3H, s, CH3),

		MH+, 297	2.60 (4H, m, 2xCH2), 3.20 (2H, t, CH2), 3.40 (4H, t, 2xCH2), 4.30 (2H, t, CH2), 8.60 (1H, s).
3	C19H20N8	ESI+, MH+, 361	(CDCl3), 2.05 (4H, m, 2xCH2), 3.20 (2H, t, CH2), 3.40 (4H, t, 2xCH2), 4.00 (4H, t, 2xCH2), 4.40 (2H, t, CH2), 6.55 (1H, t), 8.30 (2H, d), 8.65 (1H, s).
4	C17H22N6O	ESI+, MH+, 327	(CDCL3), 2.05 (4H,m, 2xCH2), 2.65 (2H, t, CH2), 2.70 (4H, m, 2xCH2), 3.20 (2H, t), 3.40 (4H, m), 3.65 (2H, t), 4.40 (2H, t), 8.60 (1H, s).
5	C23H26N6	ESI+, MH+, 387	(CDCl3), 1.80-2.00 (6H, m), 2.60 (4H, m), 3.15 (2H, m), 3.40 (4H, m), 3.60 (2H, s, CH2), 4.50 (2H, m, CH2), 7.30 (5H, m), 8.60 (1H, s).
6	C23H26N6	DCI+ NH3 MH+ 387,100%	(CDCl3): 1.97-2.13 (4H,m); 2.64-2.80 (6H,m); 2.81-2.92 (2H,m); 3.22 (2H, t, J=6.4Hz); 3.38-3.50 (4H,m); 4.45 (2H, t, J=5.5Hz); 7.16-7.36 (5H,m).
7	C26H26N6	DCI+ m/z 423 (MH+ 100%)	(CDCl3): 8.72 (1H, s); 7.66 (1H, s); 7.37 (3H, m); 7.28 (2H, m); 7.21 (3H, m); 7.09 (2H, m); 5.52 (2H, s); 3.46 (4H, br m); 2.83 (2H, m); 2.69 (6H, br m).
8	C19H20N6	DCI+ m/z 333 (MH+, 100%)	(d6dmso): 12.31 (1H, br); 8.33 (2H, s); 7.26 (5H, m); 7.18 (1H, m); 3.82 (4H, br); 2.79 (2H, m); 2.60 (6H, m)
9	C24H29N5O	DCI+NH 3 MH+ 404	(CDCl3):1.90-2.05 (4H, m), 2.66-2.75 (6H, m), 2.84-2.90 (2H, m), 2.90 (3H, s), 3.38-3.45 (6H, m), 4.42 (2H, m), 7.20-7.42 (5H, m), 8.66 (1H, s)
10	C28H35N5O	DCI+NH 3 MH+458	(CDCl3): 1.65-1.75 (4H, m), 1.80-1.90 (2H, m), 1.93-2.08 (6H, m), 2.65 -2.80 (6H, m), 2.87 (2H, t, J=7.2), 3.38 (4H, m), 3.45 (2H, t, J=6.4), 4.42 (2H, t, J=5.8), 4.58 (1H, quintet, J=8.4), 7.20-7.32 (5H, m), 8.66 (1H, s)
11	C23H28N6S	DCI+ NH3 MH+ 421	(CDCl3): 1.98-2.05 (4H, m), 2.67-2.74 (6H, m), 2.83-2.88 (2H, m), 3.42-3.48 (4H, m), 3.82-3.88 (2H, m), 4.38-4.43 (2H, m), 7.20-7.32 (5H, m), 7.44 (1H, br.s), 8.55 (1H, s), 10.95 (1H, br.s)
12	C26H30N6S	DCI+ NH3 MH+ 459	(CDCl3): 2.00-2.10 (2H, m), 2.53 (3H, s), 2.68-2.80 (6H, m), 2.87-2.91 (2H, m), 3.43-3.48 (4H, m), 3.60 (2H, t, J=6.4), 4.39 (2H, t, J=4.8), 6.88 (1H, s), 7.20-7.32 (5H, m), 8.72 (1H, s)
13	C15H18N6	CI +VE +LMR MH+283	(DMSO-d6): 1.85-2.0 (4H, m); 2.8-2.7 (4H, t, J= 4.71Hz); 3.1-3.2 (2H, t, J=6.19Hz); 3.2-3.28 (4H, t, J=4.88Hz); 4.33-4.39; 2H, t; J=5.09Hz); 8.44(1H,s)
14	C24H28N6	CI +ve +LMR MH+401. 3	(CDCl3): 1.8-1.92 (2H, m); 2.99-2.15 (4H, m); 2.39-2.50 (2H, t, J=7.62Hz); 2.59-2.72 (6H, m); 3.18-3.25 (2H, t; J=6.31Hz); 3.38-3.45 (4H, m); 4.3-4.4 (2H, t, J=5.99Hz); 7.1-7.3 (5H, m*); 8.62 (1H, s)

15	C23H24N6O	CI+ve +LMR MH+ 401	(DMSO-d6): 1.85-2.0 (4H, m); 3.1-3.2 (2H, t, J= 6Hz); 3.1-3.3 (4H, m*); 3.63-3.7 (4H, m); 3.78 (2H, s); 4.3-4.4 (2H, t; J=5.69Hz); 7.18-7.35 (5H, m); 8.5(1H, s)
16	C20H22N6	DCI+ m/z 347 (MH+, 100%)	(CDCl3): 7.90 (1H, s); 7.74 (1H, s); 7.22 (2H, m); 7.13 (3H, m); 4.91 (1H, br); 4.10 (1H, br); 4.04 (3H, s); 2.77 (2H, m); 2.59 (8H, m)
17	C27H35N5O	DCI+NH 3 MH+446	(CDCl3): 1.02 (6H, d, J=6.6), 1.90-2.04 (4H, m), 2.25-2.33 (1H, m), 2.66-2.75 (6H, m), 2.83-2.88 (2H, m), 3.26 (2H, d), 3.37-3.40 (4H, m), 3.42 (2H, t, J=6.6), 4.41 (2H, t), 7.18-7.30 (5H, m), 8.65 (1H, s)
18	C25H27N7	CI +ve +LMR MH+ 426	(DMSO-d6): 1.85-2.05 (4Hm); 2.6-2.75 (6Hm); 2.87 (2H, t, J=8.41Hz); 3.15 (2H, t, J=7.3Hz); 3.32-3.4 (4H, m); 4.32-4.4 (2H, m); 7.0 (1H, t, J=7.05Hz); 7.05 (1H, t, J=7.11Hz); 7.19 (1H, s); 7.32 (1H, d, J=8.05Hz); 7.53 (1H, d, J=7.76Hz), 8.48 (1H, s), 10.78 (1H, s)
19	C29H28N6O	CI +ve +LMR MH+ 477	(DMSO-d6): 1.85-1.97 (4H, m); 3.2-3.8 (2H, m); 3.1-3.16 (2H, t, J=6.27Hz); 3.21-3.3 (2H, m); 3.65-3.79 (4H, m); 4.35 (2H, t, J=5.76Hz); 5.58 (1H, s); 7.21-7.35 (10H, m); 8.47 (1H, s)
20	C23H24N6O	CI +ve +LMR MH+ 401	(DMSO-d6): 1.85-1.97 (4H, m); 2.7-2.76 (4H, m); 3.09-3.15 (2H, t, J=6.21Hz); 3.41-3.49 (4H, m); 3.95 (2H,s); 4.32-4.4 (2H, t, J=5.72Hz); 7.52 (2H, t, J=7.46Hz); 7.62 (1H, t, J=7.41Hz); 8.02 (2H, d, J=7.16Hz), 8.5 (1H, s)
21	C22H24N6O2S	CI +ve +LMR MH+ 437.3	(DMSO-d6): 1.85-1.97 (4H, m); 3.1-3.18 (2H, t, J=6.24Hz); 3.25-3.35 (8H,*); 3.21-3.3 (2H, m); 4.3-4.39 (2H, t, J=5.8Hz); 4.5 (2H, s); 7.32-7.45 (5H, m); 8.5(1H, s)
22	C31H32N6S	DCI+NH 3 MH+ 521	(CDCl3): 2.05-2.13 (4H, m), 2.68-2.80 (6H, m), 2.86-2.90 (2H, m), 3.40-3.46 (4H, m), 3.70-3.77 (2H, m), 4.41-4.45 (2H, m), 7.20-7.35 (6H, m), 7.45 (2H, t, J=7.8), 7.50 (1H, s), 8.04 (2H, d, J=7.3), 8.74 (1H, s)
23	C29H36N6S	DCI+NH 3 MH+ 501	(CDCl3): 1.40 (9H, s), 2.02-2.10 (4H, m), 2.65-2.75 (6H, m), 2.85-2.90 (2H, m), 3.38-3.42 (4H, m), 3.61 (2H, t, J=6.3), 4.38 (2H, t, J=5.8), 6.87 (1H, s), 7.20-7.30 (5H, m), 8.71 (1H, s)
24	C21H24N6	DCI+ m/z 361 (MH+, 100%)	(CDCl3): 7.98 (1H, s); 7.88 (1H, s); 7.31-7.19 (5H, m); 4.99 (1H, br); 4.46 (2H, q, J = 7.2 Hz); 4.14 (1H, br); 2.84 (2H, m); 2.66 (6H, m); 1.63 (3H, t, J = 7.2 Hz); 1.58 (2H, m)
25	C26H27F3N6S	DCI+NH 3 MH+ 513	(CDCl3): 2.02-2.08 (4H, m), 2.70-2.78 (6H, m), 2.85-2.90 (2H, m), 3.41-3.48 (4H, m), 4.40-4.46 (2H, m), 7.20-7.32 (5H, m), 7.69 (1H, s), 8.70 (1H, s)

26	C27H32N6S	DCI+NH 3 MH+ 473	(CDCl3): 1.98-2.10 (4H, m), 2.38 (3H, s), 2.41 (3H, s), 2.66-2.75 (6H, m), 2.82-2.90 (2H, m), 3.42 -3.48 (4H, m), 3.54 (2H, t, J=6.3), 4.35 (2H, t, J=5.1), 7.20-7.32 (5H, m), 8.71 (1H, s)
27	C27H28N6	DCI+ m/z 437 (MH+, 100%)	(d6dmso): 8.24 (1H, s); 7.94 (1H, s); 7.31-7.13 (10H, m); 4.90 (1H, br); 4.59 (2H, t, J = 7.5 Hz); 4.01 (1H, br); 3.18 (2H, t, J = 8.1 Hz); 2.77 (2H, t, J = 7.3 Hz); 2.56 (8H,m)
28	C26H29BrN6O 2S	DCI+NH 3 MH+489	(DMSO-d6): 1.98-2.05 (4H, m), 3.04-3.09 (2H, m), 3.30-3.55 (8H, m), 3.65-3.72 (2H, m), 3.86-3.91 (2H, m), 4.44-4.50 (2H, m), 7.28-7.40 (5H, m), 8.34 (1H, s), 8.65 (1H, s), 9.7 (1H, br)
29	C29H31N5O	DCI+NH 3 MH+ 466	(CDCl3): 1.95-2.02 (2H, m), 2.03-2.12 (2H, m), 2.68-2.78 (6H, m), 2.85-2.90 (2H, m), 3.37 (2H, t, J=6.7), 3.40-3.46 (4H, m), 4.46 (2H, t, J=5.6), 7.20-7.28 (3H, m), 7.30 (2H, t, J=7.4), 7.44 (2H, t, J=7.4), 7.54 (1H, t, J=7.4), 7.89 (2H, d, J=7.1), 8.51 (1H, s)
30	C23H25N7O2	CI +ve +LMR MH+ 432	(DMSO-d6): 1.87-2.0 (4H,m); 2.62-2.7 (4H,m); 2.9 (2H, t, J=7.23Hz); 3.12 (2H, t, J=6.46Hz); 3.25-3.34 (6H, m,*); 4.34 (2H, t, J=5.75Hz); 7.54 (2H, d, J=8.72Hz); 8.13 (2H, t, J=8.68Hz); 8.5 (1H, s)
31	C24H28N6O	CI +ve +LMR MH+ 417.3	(DMSO-d6): 1.88-2.01 (4H, m); 2.52-2.59 (2H, m); 2.59-2.68 (2H, m); 2.68-2.74 (2H, m); 3.12 (2H, t, J=6.22Hz); 3.2-3.4 (6H, m); 3.69 (3H, s); 4.35 (2H, t, J=5.05Hz) 6.82 (2H, d, J=8.66Hz); 7.16 (2H, t, J=8.6Hz); 8.45 (1H,s)
32	C23H32N6	CI +ve +LMR MH+ 393.3	(CDCl3): 0.89-1.01 (2H, m); 1.11-1.36 (4H, m); 1.39-1.46 (2H, m); 1.63-1.78 (2H, m); 1.97-2.11 (4H, 2m); 2.4-2.48 (2H, m); 2.55-2.69 (4H, m); 3.19 (2H, t, J=6.26Hz); 3.39 (4H, d, J=4.67Hz); 4.32 (2H, t, J=5.08Hz); 8.62 (1H, s)
33	C25H28N6S	DCI+NH 3 MH+445	(CDCl3): 2.00-2.10 (4H, m), 2.66-2.75 (6H, m), 2.82-2.90 (2H, m), 3.38-3.45 (4H, m), 3.55 (2H, t, J=6.1), 4.38 (2H, t, J=4.7), 7.18-7.30 (5H, m), 7.30 (1H, d, J=3.4), 7.83 (1H, d, J=3.4), 8.72 (1H, s)
34	C27H28N6	CI +ve +LMR MH+437	(CDCl3): 1.99-2.12 (4H, m); 2.72-2.87 (6H, m); 3.21 (2H, t, J=6.31Hz); 3.33 (2H, t, J=8.26Hz); 3.46 (4H, t, J=4.72Hz); 4.35 (2H, t, J=5.29Hz); 7.35-7.56 (4H, m); 7.75 (1H, d, J=7.78Hz); 7.88 (1H, d, J=7.69Hz); 8.08 (1H, d, J=8.25Hz); 8.63 (1H, s)
35	C24H28N6	MH+ @401	(Chloroform): 8.62 (s,1H), 7.35-7.10 (m, 5H), 4.33 (m, 2H), 3.51 (m, 2H), 3.30-2.60 (m, 13H), 2.04 (m, 4H), 1.05 (d, 3H).
36	C24H25F3N6	DCI+ NH3 MH+ 455	(CDCl3): 1.94-2.14 (4H,m); 2.62-2.82 (6H,m); 2.83-2.98 (2H,m); 8.13-3.27 (2H,m); 3.34-3.52 (4H,m); 4.28-4.40 (2H,m); 7.37-7.55 (4H,m); 8.62 (1H,s).

		(100%)	
37	C23H25ClN6	DCI+ NH3 MH+ 421 (100%)	(CDCl3): 1.88-2.18 (4H,m); 2.48-2.98 (8H,m); 3.10-3.52 (6H,m); 4.22-4.42 (2H,m); 7.00-7.35 (4H,m); 8.60 (1H,s)
38	C23H25N7O2	DCI+ NH3 MH+ 432 (100%)	(CDCl3): 1.99-2.15 (4H, m); 2.69-2.83 (6H, m); 2.96 (2H, t, J=7.6Hz); 3.20 (2H, t, J=6.4Hz); 3.38-3.58 (4H,m); 4.36 (2H, t, J=5.6Hz); 7.47 (1H, t, J=7.9Hz); 7.59 (1H, d, J=7.6Hz); 8.10 (2H, t, J=8.0Hz); 8.62 (1H, s).
39	C24H28N6	CI +ve +LMR MH+ 401.3	(CDCl3): 1.99-2.12 (4H, m); 2.35 (3H, s); 2.59-2.65 (2H, m); 2.67-2.78 (4H, m(broad)); 2.8-2.9 (2H, m); 3.2 (2H, t, J=6.36Hz); 3.42 (4H, t, J=4.79Hz); 4.35 (2H, t, J=5.9Hz); 7.1-7.2 (4H, m); 8.61 (1H, s);
40	C23H25FN6	CI +ve +LMR MH+ 405.3	(CDCl3): 1.99-2.12 (4H, m); 2.65-2.8 (6H, m); 2.88 (2H, t, J=7.17Hz); 3.21 (2H, t, J=6.35Hz); 3.42 (4H, t, J=4.79Hz); 4.35 (2H, t, J=5.9Hz); 6.9-7.1 (2H, m); 7.15-7.21 (2H, m); 8.61 (1H, s);
41	C22H31N7	(DCI) MH+ 394	(CDCl3): 1.37-1.40 (2H, m), 1.49-1.56 (4H, m), 2.43-2.60 (12H, m), 3.12 (2H, t, J=6.5), 3.32 (4H, t, J=4.6), 4.26 (2H, t, J=5.2), 8.54 (1H, s)
42	C23H33N7	(DCI) MH+408	(CDCl3): 1.49-1.55 (6H, m), 1.62-1.70 (2H, m), 1.94-2.01(4H, m), 2.25-2.38 (8H, m), 2.55 (4H, m), 3.12 (2H,t), 3.32(4H, t), 4.23-4.28 (2H, m), 8.55 (1H, s)
43	C24H27N5	DCI MH+ 386 (100%)	(CDCl3): 1.90-2.01 (4H, m), 2.62-2.70 (6H, m), 2.75-2.80 (2H, m), 3.07 (2H, t), 3.33 (1H, s), 3.35-3.40 (4H, m), 4.19 (2H, t), 7.12-7.25 (5H, m), 8.54 (1H, s).
44	C21H24N6	DCI+ NH3 MH+ 361 (100%)	(CDCl3): 2.54 (3H, s); 2.59-2.72 (6H, m); 2.74-2.83 (2H, m); 3.31-3.39 (4H, m); 3.86 (3H, s); 7.10-7.28 (5H, m); 8.54 (1H, s).
45	C24H28N6	DCI+ NH3 MH+ 401 (100%)	(CDCl3): 1.41 (3H, d, J=6.9Hz); 2.10-2.17 (4H, m); 2.64-2.78 (6H, m); 3.06-3.11 (1H, m); 3.29 (2H, t, J=6.3Hz); 3.45 (4H, m); 4.43 (2H, t, J=5.5Hz); 7.30-7.43 (5H, m); 8.71 (1H, s).
46	C23H29N5O	DCI MH+ 392 (100%)	(CDCl3): 2.02-2.16 (4H, m), 2.80-2.90 (6H, m), 2.95-3.00 (2H, m), 3.13 (2H, t), 3.55-3.60 (4H, m), 4.30 (2H, t), 4.96 (2H, s), 7.30-7.42 (5H, m), 8.65 (1H, s).
47	C28H38N6	DCI MH+ 459(80%)	(CDCl3): 1.30-1.38 (2H, m), 1.45-1.52 (4H, m), 1.80-1.88 (2H, m), 1.88-1.98 (2H, m), 2.35-2.41 (4H, m), 2.60-2.70 (6H, m), 2.75-2.80 (2H, m), 2.98 (2H, t), 3.31-3.39 (4H, m), 3.59 (2H, s), 4.12 (2H, t), 7.10-7.22 (5H, m), 8.50 (1H, s).
48	C24H25N7	DCI+ NH3 MH+ 412	(CDCl3): 1.93-2.01 (4H, m); 2.59-2.63 (6H, m); 2.82 (2H, t, J=7.6Hz); 3.12 (2H, t, J=6.4Hz); 3.32-3.35 (4H, m); 4.27 (2H, t, J=5.5Hz); 7.26 (2H, d, J=8.2Hz);

		(100%)	7.51 (2H, d, J=8.2Hz); 8.55 (1H, s).
49	C23H25IN6	M+H 513	(CDCl3): 1.90-2.00 (4H, m), 2.60-2.65 (6H, m), 2.75 (2H, m), 3.10 (2H, t), 3.35-3.40 (4H, m), 4.20 (2H, t), 7.10-7.30 (5H, m)
50	C23H29N7O	(DCI) MH+ 420	(CDCl3),: 1.83-1.95 (4H, m), 2.60-2.65 (6H, m), 2.72-2.80 (2H, m), 3.21 (2H, t, J=6.7), 3.35 (4H, t, J=4.4),4.25 (2H, t, J=5.3), 6.40 (2H, br. s), 7.12-7.25 (5H, m), 8.45 (1H, s)
51	C28H32N6O2S	(DCI) MH+ 517	(CDCl3): 1.35 (3H, t, J=7.1), 1.98 (4H, m), 2.61-2.68 (6H, m), 2.78-2.82 (2H, m), 3.38 (4H, m), 3.59 (2H, t, J=6.0), 4.32-4.38 (4H, m), 7.15-7.25 (5H, m), 8.07 (1H, s), 8.65 (1H, s)
52	C23H28N6O	(DCI) MH+ 405	(CDCl3): 1.95-2.00 (4H, m), 2.57-2.68 (6H, m), 2.75-2.83 (2H, m), 3.33-3.40 (4H, m), 3.45 (2H, t, J=6.3), 4.30 (2H, t, J=5.8), 5.40 (1H, br. s), 7.12-7.28 (5H, m), 8.50 (1H, s), 8.72 (1H, br. s)
53	C27H26F2N6		(CDCl3) 8.47 (1H, s); 6.95 (8H, m); 4.17 (2H, s); 3.62 (3H, s); 3.18 (4H, bs); 2.51 (8H, m)
54	C24H26N6	DCI MH+ 399 (100%)	(CDCl3) 1.90-2.02 (4H, m), 2.60-2.70 (4H, b), 2.82-2.90 (2H, m), 3.00-3.21 (5H, m), 3.33-3.40 (4H, broad), 4.28 (2H, t), 7.08-7.15 (4H, m), 8.5(1H, s)
55	C29H30N6	MH+ @463	(CHCl3) 8.55 (d, 2H), 7.47-7.22 (m, 8H), 4.34 (t, 2H), 3.51 (m, 4H), 3.21 (t, 2H), 2.88 (m, 2H), 2.75 (m, 6H), 2.15-1.95 (m, 4H)
56	C24H27ClN6O2	DCI+ NH3 free base MH+ 431 (100%)	(d6-dmso) 1.92-1.95 (4H, m); 3.12-3.20 (4H, m); 3.31-3.55 (6H, m); 3.62-3.74 (2H, m); 3.82-3.85 (2H, m); 4.38-4.40 (2H, m); 7.40 (2H, d, J=8.1Hz); 7.91 (2H, d, J=8.0Hz); 8.4 (1H,s); 11.08 (1H, broad peak); 12.90 (1H,broad peak).
57	C26H32N6O3	DCI MH+ 477 (100%)	(CDCl3) 1.95-2.05 (4H, m); 2.63-2.75 (6H, m); 2.78-2.82 (2H, m); 3.20 (2H, t); 3.41-3.45 (4H, m); 3.85 (3H, s); 3.87 (6H, s) 4.34 (2H, t); 6.45 (2H, s); 8.65 (1H, s).
58	C25H30N8	MH+ 443	(CDCl3): 2.05-2.15 (4H, m), 2.50 (3H, s), 2.68-2.80 (6H, m), 2.85-2.92 (2H, m), 3.45-3.50 (4H, br. m), 3.56 (2H, t, J=6.4), 4.38 (2H, t, J=5.8), 7.20-7.30 (5H, m), 8.60 (1H, s), 12.48 (1H, br. s)
59	C23H27N7	DCI +ve MH+ 402 (100%)	(CDCl3): 1.95-2.10 (4H, m); 2.62-2.80 (8H, m); 3.20 (2H, t, J=6.4Hz); 3.42 (4H, m); 4.34 (2H, t, J=5.8Hz); 6.54 (1H, d); 6.56 (1H, s); 6.60 (1H, d, J=7.6Hz); 7.08 (1H, t, J=7.8Hz); 8.60 (1H, s).
60	C29H34N6O2S	DCI +ve MH+ 531 (100%)	(CDCl3) 2.04-2.18 (4H, m); 2.49 (3H, s); 2.50 (3H, s); 2.76-2.90 (6H, m); 3.02 (2H, dd, J=7.9Hz); 3.48-3.56 (4H, m); 3.63 (2H, t, J=6.3Hz); 4.02 (3H, s); 4.46 (3H, t, J=5.4Hz); 7.46 (1H, t, J=7.6Hz); 7.54 (1H, d, J=7.6Hz); 7.99 (1H, s); 8.01(1H, d, J=5.6Hz);

			8.81 (1H, s).
61	C27H31N7O2S	MH+ 518	(CDCl3): 1.93-2.07 (4H, m), 2.34 (3H, s), 2.36 (3H, s), 2.65-2.78 (6H, m), 2.90-2.97 (2H, m), 3.40 (4H, br), 3.53 (2H, t, J=6.5), 4.35 (2H, t, J=5.8), 7.45 (1H, t, J=7.8), 7.55 (1H, d, J=7.8), 8.06 (1H, d, J=7.8), 8.0 (1H, s), 8.68 (1H, s)
62	C30H32N6O	m/z 493 (MH+, 100%)	(CDCl3): 8.07 (2H, m); 7.33-7.16 (6H, m); 6.91 (1H, m); 4.29 (2H, m); 3.86 (3H, s); 3.42 (4H, m); 3.13 (2H, m); 2.80 (2H, m); 2.63 (6H, m); 1.95 (4H, m).
63	C29H29N7O2	MH+ 508	(DMSO) 8.67 (d, 2H), 8.48 (d, 2H), 7.35-7.19 (m, 5H), 4.40 (t, 2H), 3.52 (m, 4H), 3.19 (t, 2H), 2.84 (t, 2H), 2.71 (m, 4H), 2.64 (t, 2H), 1.99 (m, 4H).
64	C23H24F2N6	CI +ve +LMR MH+ 423.3	(CDCl3) 1.92-2.12 (4H, m); 2.55-2.7 (6H, m(broad)); 2.72-2.82 (2H, m); 3.2 (2H, t, J=6.36Hz); 3.42 (4H, t, J=4.79Hz); 4.35 (2H, t, J=5.9Hz); 6..83-6.93 (1H, m); 6.98-7.1 (2H, m); 8.61 (1H, s);
65	C23H24F2N6	CI +ve +LMR MH+ 423.3	(D6DMSO) 1.95-2.1 (4H, m); 2.68-2.8 (4H, m); 2.86-2.95 (2H, broad); 3.18-3.25 (2H, broad); 4.42-4.49 (2H, broad); 7.1-7.2 (3H, m); 8.58 (1H, s) *6H OBSCURED UNDER 6H-DMSO PEAK
66	C23H24F2N6	CI +ve +LMR MH+ 423.3	(D6DMSO) 1.95-2.1 (4H, m); 2.46-2.73 (4H, m); 2.86-2.95 (2H, broad); 3.18-3.25 (2H, broad); 4.32-4.43 (2H, broad); 7.1-7.35 (3H, m); 8.5 (1H, s) *6H OBSCURED UNDER 6H-DMSO PEAK
67	C23H24Cl2N6	CI +ve +LMR MH+ 457.1, 456.1, 455.1	(D6DMSO) 1.85-2.2 (4H, m); 2.58-2.73 (4H, m); 2.86-2.95 (2H, (broad)); 3.18-3.25 (2H, (broad)); 4.32-4.43 (2H, (broad)); 7.35-7.5 (2H, m); 7.6 (1H, s); 8.5 (1H, s) *6H OBSCURED UNDER 6H-DMSO PEAK
68	C29H31N7	MH+ @ 478	(D6DMSO) 8.08 (d, 2H), 7.30-7.15 (m, 5H), 6.59 (d, 2H), 5.50 (br.s, 2H), 4.32 (t, 2H), 3.36 (m, 4H), 3.10 (t, 2H), 2.79 (t, 2H), 2.65 (m, 4H), 2.60 (t, 2H), 1.93 (m, 4H).
69	C31H33N7O	MH+ @520	(DMSO) 10.12 (br.s,1H), 8.32 (d, 2H), 7.69 (d, 2H), 7.30-7.14 (m, 5H), 4.33 (t, 2H), 3.39 (m, 4H), 3.08 (t, 2H), 2.75 (t, 2H), 2.64 (m, 4H), 2.60 (m, 2H), 2.09 (s, 3H), 1.90 (m, 4H).
70	C36H35N7O	MH+ @582	(DMSO) 10.43 (br.s, 1H), 8.37 (d, 2H), 8.13 (d, 2H), 7.98 (d, 2H), 7.90 (d, 2H), 7.81 (t, 1H), 7.65-7.45 (m, 5H), 7.30-7.14 (m, 5H), 4.34 (t, 2H), 3.49 (m, 2H), 3.12 (t, 2H), 3.06 (m, 2H), 2.82-2.60 (m, 4H), 1.91 (m, 4H), 1.14 (t, 2H).
71	C35H34N8O	MH+ @583	(DMSO) 10.62 (br.s, 1H), 8.99 (d, 2H), 8.62 (d, 2H), 8.06 (m, 3H), 7.45 (m, 7H), 4.68 (t, 2H), 3.75 (m, 2H), 3.31 (t, 2H), 2.93 (t, 2H), 2.86 (m, 2H),

			2.80 (m, 2H), 1.90 (m, 4H), 1.12 (t, 2H).
72	C25H29F2N7	[M + H]+ 466.4	(CDCl3) 8.67 (1H, s), 7.23-7.13 (2H, m), 7.06 (1H, m), 4.47 (2H, t, J 5.6), 3.87 (4H, s, br), 3.61 (2H, t, J 6.4), 3.54 (4H, s, br), 2.94 (2H, t, J 6.3), 2.84 (4H, s. br), 2.79 (2H, t, J 6.2), 2.15 - 2.06 (4H, m)
73	C23H28F2N6O	DCI +ve MH+ 443 (100%)	(CDCl3) 1.40 (6H, d); 2.54-2.70 (6H, m); 2.71 (2H, t); 3.30 (4H, m); 3.90 (3H, s); 4.40 (1H, septet), 5.40 (1H, brs), 6.80-6.84 (1H, m), 6.92-7.0 (2H, m); 8.52 (1H, s), 9.1 (H, brs)
74	C27H30F2N6S	MH+ 509	(CDCl3): 2.00-2.10 (4H, m), 2.38 (3H, s), 2.40 (3H, s), 2.65-2.74 (6H, m), 2.79-2.83 (2H, m), 3.42 (4H, br), 3.56 (2H, t, J=6.2), 4.37 (2H, t, J=5.5), 6.90-6.98 (1H, m), 7.05-7.10 (2H, m), 8.71 (1H, s)
75	C25H29N7O	DCI +ve MH+ 444 (100%)	(CDCl3) 1.95-2.10 (4H,m); 2.18 (3H,s); 2.60-2.78 (6H,m); 2.80-2.88 (2H,m); 3.20 (2H,t,6.6Hz); 3.40 (4H,m); 4.34 (2H,t,5.6Hz); 6.96 (1H,s); 7.16-7/30 (3H,m); 7.52 (1H,s); 8.60 (1H,s).
76	C24H29N7O2S	DCI +ve MH+ 480 (100%)	(CDCl3) 1.96-2.06(4H,m); 2.54-2.68(6H,m); 2.74-2.80(2H,m); 2.96(3H,s); 3.12(2H,t,J=6.5Hz); 3.30-3.40(4H,m); 4.30(2H,t,J=5.7Hz); 6.40(1H,br s); 6.99(2H,dd,J=4.3,7.8Hz); 7.07(1H,s); 7.20(1H,t); 8.56(1H,s).
77	C26H30N6S	MH+ 459	(CDCl3): 1.92-2.02 (4H, m), 2.45 (3H, s), 2.63-2.72 (6H, m), 2.80-2.84 (2H, m), 3.38 (4H, br), 3.48 (2H, t, J=6.2), 4.33 (2H, t, J=5.5), 7.15-7.25 (5H, m), 7.42 (1H, s), 8.66 (1H, s)
78	C25H29N7O	MH+ 444	(CDCl3): 2.00-2.14 (4H, m), 2.70 (3H, s), 2.70-2.80 (6H, m), 2.83-2.92 (2H, m), 3.40-3.52 (2H+4H, m), 4.40 (2H, t, J=6.0), 7.20-7.33 (5H, m), 8.77 (1H, s)
79	C26H31N7S	ESI+, MH+ 474	(CDCl3) 1.95 (4H, m, 2xCH2), 2.30 (6H, s+s, 2xCH3), 2.65 (6H, m, 2xCH2), 2.80 (2H, m, CH2), 3.35 (4H, m, 2xCH2), 3.50 (2H, t, CH2), 4.30 (2H, t, CH2), 7.10 (2H, d), 8.42 (2H, d), 8.65 (1H, s).
80	C25H32N6O	MH+ 433	(CDCl3): 1.28 (3H, t, J=7.2), 1.90-2.03 (4H, m), 2.65-2.77 (6H, m), 2.86-2.92 (2H, m), 3.40 (4H, br), 3.50-3.60 (4H, m), 4.34 (2H, t, J=5.8), 7.20-7.30 (5H, m), 8.53 (1H, s), 8.90 (1H, t)
81	C25H32N6S	MH+ 449	(CDCl3): 1.38 (3H, t, J=7.2), 1.92-1.96 (4H, m), 2.60-2.70 (6H, m), 2.80-2.86 (2H, m), 3.33 (4H, br. m), 3.80-3.88 (4H, m), 4.32 (2H, br. m), 7.15-7.28 (5H, m), 8.48 (1H, s),11.5 (1H, br)
82	C30H34N6O	MH+ 495	(CDCl3): 1.88-2.00 (4H, m), 2.60-2.70 (6H, m), 2.78-2.82 (2H, m), 3.33 (4H, br. m), 3.50 (2H, t, J=6.6), 4.28 (2H, t, J=5.8), 4.76 (2H, d, J=5.9), 7.15-7.28 (8H, m), 7.32 (2H, d, J=7.4), 8.45 (1H, s), 9.35 (1H, t)
83	C29H33N7O	MH+ 496	(CDCl3): 1.90-2.05 (4H, m), 2.60-2.75 (6H, m), 2.80-

			2.86 (2H, m), 3.35 (4H, br. m), 3.50 (2H, t, J=6.4), 4.28 (2H, t, J=5.8), 4.68 (2H, d, J=6.0), 7.15-7.25 (6H, m), 7.68 (1H, d, J=7.9), 8.44 (1H, d, J=3.3), 8.45 (1H, s), 8.60 (1H, s), 9.40 (1H, t)
84	C30H40N6O	MH+ 501	(CDCl3): 0.70-0.80 (2H, m), 0.85-0.91 (2H, m), 0.99 (2H, t, J=11.7), 1.14-1.20 (2H, m), 1.55-1.64 (1H, m), 1.65-1.72 (2H, m), 1.80 (2H, d, J=12.5), 1.85-2.00 (4H, m), 2.60-2.72 (6H, m), 2.80 (2H, m), 3.28 (2H, t, J=6.4), 3.35 (4H, br. m), 3.50 (2H, t, J=6.7), 4.27 (2H, t, J=5.9), 7.15-7.25 (5H, m), 8.50 (1H, s), 8.96 (1H, t)
85	C27H33N7	MH+456	(CDCl3): 1.88-2.00 (4H, m), 2.15 (3H, s), 2.19 (3H, s), 2.60-2.70 (6H, m), 2.78-2.82 (2H, m), 3.35 (4H, br. m), 3.50 (2H, t, J=6.2), 4.22 (2H, t, J=5.9), 7.15-7.25 (5H, m), 8.50 (1H, s)
86	C28H29Cl2F2N7	free base - m/z 500.4 (MH+, base peak)	(d6dmso) 10.94 (1H, m); 8.73 (2H, m); 8.42 (2H, m); 7.24 (3H, m); 6.99 (1H, m); 4.26 (3H, m); 3.88 (3H, m); 3.48-2.92 (14H, m).
87	C25H32N6O	MH+ 433	(CDCl3): 2.08-2.15 (2H, m), 2.18-2.21 (2H, m), 2.70 (3H, s), 2.85-2.95 (6H, m), 3.04-3.10 (2H, m), 3.40 (2H, t, J=6.6), 3.55 (4H, br. m), 4.14 (3H, s), 4.48 (2H, t, J=5.9), 7.38-7.50 (5H, m), 8.78 (1H, s)
88	C31H36N6O	MH+ 509	(CDCl3): 1.73-1.80 (2H, m), 1.88-1.95 (2H, m), 2.51 (3H, s), 2.60-2.70 (6H, m), 2.75-2.80 (2H, m), 2.95 (2H, t, J=6.6), 3.30 (4H, br. m), 4.20 (2H, t, J=5.8), 5.11 (2H, s), 7.12-7.25 (6H, m), 7.28 (2H, t, J=7.6), 7.32 (2H, d, J=7.3), 8.50 (1H, s)
89	C23H31Cl2N7	MH+ 404 (for free base)	(DMSO-d6):1.75-1.82 (4H, m), 2.95-3.00 (2H, m), 3.15-3.25 (6H, m), 3.38 (2H, t, J=12.5), 3.48 (2H, d, J=11.8), 3.70 (2H), 4.30 (2H, br), 7.10-7.20 (5H, m), 8.45 (1H, s), 8.52 (2H,br), 8.72 (2H,br), 11.38(1H, br)
90	C31H36N6O	MH+ 509	(CDCl3): 1.90-2.00 (4H, m), 2.38 (3H, s), 2.64-2.70 (6H, m), 2.80-2.86 (2H, m), 3.38 (4H, br.m), 3.52 (2H, t, J=6.4), 4.30 (2H, t, J=5.8), 4.63 (2H, d, J=5.8), 7.10-7.25 (8H, m), 7.32-7.35 (1H, m), 8.45 (1H, s), 9.28 (1H, t)
91	C28H27F2N7	m/z 500.4 (MH+, 100%)	(CDCl3) 9.61 (1H, s); 8.71 (1H, m); 8.59 (1H, dd, J = 4.8 & 1.7 Hz); 7.32 (1H, m); 7.00 (2H, m); 6.87 (1H, m); 4.29 (2H, m); 3.45 (4H, m); 3.13 (2H, m); 2.74 (2H, m); 2.63 (6H, m); 1.99 (4H, m).
92	C30H32N6S	DCI +ve MH+ 509 (100%)	(CDCl3) 1.80-1.94 (4H, m); 2.23 (3H, s); 2.27 (3H, s); 2.48-2.66 (4H, m); 3.20-3.32 (4H, m); 3.39 (2H, t, J=6.4Hz); 3.63 (2H, s); 4.22 (2H, t, J=5.4Hz); 7.30-7.38 (2H, m); 7.41 (1H, d, J=8.1Hz); 7.64 (1H, s); 7.66-7.74 (3H, m); 8.57 (1H, s).

93	C29H31N7S	DCI MH+ 510 (100%)	(CDCl3) 2.01-2.10 (4H,m); 2.41 (3H,s), 2.43 (3H,s), 2.82-2.84 (4H,m); 3.41-3.45 (4H,m); 3.55 (2H,t); 4.01 (2H,s), 4.44 (2H,t); 7.60-7.62 (1H,m), 7.75-7.80 (2H,m), 7.90-7.92 (1H,m), 8.15-8.16 (1H,m), 8.23-8.24 (1H,m), 8.78 (1H,s)
94	C30H33ClN6O	MH+ 529:531 3:1	(CDCl3): 1.92-2.02 (4H, m), 2.65-2.73 (6H, m), 2.82-2.88 (2H, m), 3.40 (4H, br. m), 3.53 (2H, t, J=6.7), 4.35 (2H, t, J=5.9), 4.78 (2H, d, J=6.2), 7.15-7.30 (7H, m), 7.32 (1H, d, J=7.3), 7.48 (1H, d, J=7.0), 8.55 (1H, s), 9.48 (1H, t)
95	C25H30N6S2	DCI MH+ 479 (100%)	(CDCl3) 2.01-2.10 (4H,m); 2.39 (3H,s), 2.40 (3H,s), 2.70-2.74 (6H,m); 3.00 (2H,t), 3.41-3.45 (4H,m); 3.50 (2H,t); 4.30 (2H,t); 6.80-6.82 (1H,m), 6.89-6.90 (1H,m), 7.09-7.11 (1H,m), 8.67 (1H,s)
96	C31H36N6O2	MH+ 525	(CDCl3): 1.90-2.02 (4H, m), 2.63-2.70 (6H, m), 2.78-2.86 (2H, m), 3.36 (4H, br. m), 3.52 (2H, t, J=6.6), 3.88 (3H, s), 4.30 (2H, t, J=5.9), 4.66 (2H, d, J=6.1), 6.82-6.90 (2H, m), 7.18-7.28(6H, m), 7.35 (1H, d, J=7.4), 8.52 (1H, s), 9.45 (1H, t)
97	C26H24F2N6	MH+ 459.5	(DMSO) 8.61 (1H, s) ; 7.55 (5H, m) ; 6.94 (3H, m) ; 3.78 (3H, s) ; 3.48 (4H, bs) ; 2.61 (8H, m).
98	C24H26F2N6	DCI+ m/z 437.3 (MH+, 100%)	(CDCl3) 8.42 (1H, s); 6.91 (2H, m); 6.76 (1H, m); 4.17 (2H, m); 3.39 (2H, m); 3.14 (1H, m); 3.02 (2H, m); 2.85 (3H, m); 2.62 (3H, m); 2.49 (2H, m); 1.89 (4H, m).
99	C24H29N5O2	MH+ 420	(CDCl3): 1.90-2.00 (4H, m), 2.60-2.70 (6H, m), 2.78-2.82 (2H, m), 3.29-3.38 (6H, m), 3.91 (3H, s), 4.35 (2H, t, J=5.8), 7.12-7.25 (5H, m), 8.68 (1H, s)
100	C22H23N7O	DCI+, MH+, 402.1	(CDCl3), 2.15 (4H, m, 2xCH2), 3.30 (2H, t, CH2), 3.55 (4H, m,), 3.70 (4H, m), 4.50 (2H, t, CH2), 6.65 (1H, s, NH), 7.20-7.45 (5H, m), 8.75 (1H, s).
101	C29H33N7S	DCI +ve MH+ 512 (100%)	(CDCl3) 1.48-1.60 (4H,m); 1.90 (3H,s); 1.93 (3H,s); 2.18-2.34 (4H,m); 2.88-3.00 (4H,m); 3.05 (2H, t, J=6.3Hz); 3.34 (2H, dd, J=5Hz); 3.88 (2H, t, J=5.4Hz); 6.58 (1H, s); 6.68 (1H, t, J=7.4Hz); 6.89 (1H, d, J=7.1Hz); 6.86 (1H, d, J=8.1Hz); 7.30 (1H, d, J=8.0Hz); 8.22 (1H,s).
102	C28H32N6O2S	DCI +ve MH+ 517 (100%)	(CDCl3) 2.04-2.16 (4H,m); 2.47 (3H,s); 2.49 (3H,s); 2.65-2.80 (4H,m); 3.40-3.54 (4H, m); 3.58 (2H,s); 3.60 (2H, t, J=6.3Hz); 4.34 (4H, s); 4.42 (2H, t, J=5.4Hz); 6.90 (2H, s); 6.97 (1H, s); 8.79 (1H, s).
103	C30H37N7OS	DCI +ve MH+ 544 (100%)	(CDCl3) 2.00-2.14 (4H,m); 2.44 (3H,s); 2.26 (3H,s); 2.70-2.84 (6H,m); 2.94 (2H,t,J=8.2Hz); 3.05 (3H,s); 3.18 (3H,s); 3.40-3.50 (4H,m); 3.60 (2H,t,J=6.3Hz); 4.40 (2H,t,J=5.4Hz); 7.27-7.40 (4H,m); 8.78 (1H,s).
104	C18H23N7O	DCI+,	(d6-DMSO) 0.85 (3H, t, CH3), 1.80 (4H, m, 2xCH2),

		MH+, 354.2	2.90 (4H, m, 2xCH2), 3.10 (4H, m, 2xCH2), 3.30 (4H, m, 2xCH2), 4.25 (2H, t, CH2), 6.45 (1H, t, NH), 8.35 (1H, s, PyrmH).
105	C32H38N6O3	MH+ 555	(CDCl3): 2.00-2.10 (4H, m), 2.75-2.82 (6H, m), 2.90-2.95 (2H, m), 3.44 (4H, br. m), 3.62 (2H, t, J=6.6), 3.93 (3H, s), 4.00 (3H, s), 4.38 (2H, t, J=5.7), 4.80 (2H, d, J=6.0), 6.85 (2H, d, J=7.7), 7.03-7.12 (2H, m), 7.25-7.38 (5H, m), 8.55 (1H, s), 9.44 (1H, t)
106	C28H33N7OS	DCI +ve MH+ 516 (100%)	(CDCl3) 2.00-2.18 (4H, m); 2.43 (3H, s); 2.47 (3H, s); 2.70-2.88 (4H, m); 2.98 (2H, t, J=7.9Hz); 3.5 (4H, m); 3.58 (2H, t, J=6.4Hz); 4.44 (2H, t, J= 5.5Hz); 7.40-7.52 (2H, m); 7.69 (1H, d, J=7.3Hz); 7.80 (1H, s); 8.77 (1H, s).
107	C29H31N7S	DCI MH+ 510 (100%)	(CDCl3) 2.01-2.10 (4H, m); 2.41 (3H, s), 2.43 (3H, s), 2.82-2.84 (4H, m); 3.41-3.45 (4H, m); 3.55 (2H, t); 4.01 (2H, s), 4.44 (2H, t); 7.48-7.50 (1H, m), 7.60-7.61 (1H, m), 7.75-7.77 (1H, m), 8.15 (1H, d), 8.32 (1H, d) 8.72 (1H, s), 8.90-8.92 (1H, m).
108	C31H33N7O	MH+ 520	(CDCl3) 1.96-2.08 (4H, m), 2.62-2.70 (6H, m), 2.82-2.88 (2H, m), 3.40 (4H, br. m), 3.53 (2H, t, J=6.6), 4.32 (2H, t, J=5.9), 4.70 (2H, d, J=6.1), 7.18-7.28 (5H, m), 7.37 (1H, t, J=7.8), 7.48 (1H, d, J=7.8), 7.60 (1H, d, J=7.8), 7.64 (1H, s), 8.50 (1H, s), 9.50 (1H, t)
109	C28H30N6S2	DCI MH+ 515 (100%)	(CDCl3) 2.01-2.10 (4H,m); 2.41 (3H, s), 2.43 (3H, s), 2.72-2.74 (4H, m); 3.41-3.45 (4H, m); 3.55 (2H, t); 3.81 (2H, s), 4.40 (2H, t); 7.25-7.36 (3H, m), 7.80-7.81 (1H, m), 8.00-8.01 (1H, m), 8.72 (1H, s)
110	C29H33N7O	MH+ 496	(CDCl3): 1.95-2.08 (4H, m), 2.68-2.77 (6H, m), 2.82-2.90 (2H, m), 3.45 (4H, br. m), 3.56 (2H, t), 4.35 (2H, t), 4.88 (2H, d, J=6.0), 7.15-7.20 (1H, m), 7.22-7.32 (5H, m), 7.40 (1H, d, J=7.9), 7.61-7.68 (1H, m), 8.56 (1H, s), 8.57 (1H, d), 9.65 (1H, t)
111	C28H31N7S	DCI MH+ 498 (100%)	(CDCl3) 2.01-2.10 (4H,m); 2.31 (3H,s), 2.33 (3H,s), 2.72-2.74 (4H, m); 3.41-3.45 (4H, m); 3.50 (2H,t); 3.75 (2H, s), 4.26 (2H, t); 7.05-7.15 (3H, m), 7.30 (1H, d), 7.71 (1H,d), 8.10 (1H,s,broad), 8.62 (1H,s)
112	C32H36N6O3	MH+ 553	(CDCl3): 1.95-2.10 (4H, m), 2.70-2.80 (6H, m), 2.85-2.91 (2H, m), 3.45 (4H, br. m), 3.57 (2H, t, J=6.4),3.90 (3H, s), 4.38 (2H, t, J=5.3), 4.78 (2H, d, J=6.0), 7.20-7.33 (5H, m), 7.48 (2H, d, J=8.3), 8.00 (2H, d, J=8.3), 8.54 (1H, s), 9.50 (1H, t, J=6.0)
113	C28H30N6OS	DCI +ve MH+ 499 (100%)	(CDCl3) 1.80-1.98 (4H, m); 2.28 (3H, s); 2.30 (3H, s); 2.56-2.74 (4H, m); 3.33 (4H, m); 3.40 (2H, t, J=6.2Hz); 3.70 (2H, s); 4.22 (2H, t, J=5.9Hz); 6.55 (1H, s); 7.10-7.20 (2H, m); 7.40 (1H, d, J=8.1Hz); 7.44 (1H, d, J=7.3Hz); 8.60 (1H, s).

114	C27H30N6O2S	DCI +ve MH+ 503 (100%)	(CDCl3) 1.90-2.05 (4H, m); 2.33 (3H, s); 2.36 (3H, s); 2.52-2.70 (4H, m); 3.28-3.42 (4H, m); 3.44-3.54 (4H, m); 4.32 (2H, t, J=5.4Hz); 5.92 (2H, s); 6.75 (2H, m); 6.88 (1H, s); 8.67 (1H, s).
115	C28H31N7S	DCI MH+498 (100%)	(CDCl3) 2.01-2.10 (4H, m); 2.41 (3H, s), 2.43 (3H, s), 2.82-2.84 (4H, m); 3.41-3.45 (4H, m); 3.55 (2H, t); 3.67 (2H, s), 4.40 (2H, t); 6.45-6.47 (1H, m), 7.10-7.25 (2H, m), 7.40 (1H, d), 7.55 (1H, s), 8.10 (1H, s, broad) , 8.72 (1H, s)
116	C29H35N7OS	MH+ 530 (100%)	(CDCl3) 1.85-2.00 (4H, m); 2.31 (3H, s); 2.32 (3H, s); 2.55-2.72 (6H, m); 2.80 (2H, t, J=7.8Hz); 2.95 (3H, d, J=4.8Hz); 3.26-4.40 (4H, m); 3.45 (2H, t, J=6.3Hz); 4.29 (2H, t, J=5.3Hz); 6.08 (1H,broad peak); 7.24-7.32 (2H, m); 7.49 (1H, d, J=6.3Hz); 7.60 (1H, s); 8.64 (1H, s).
117	C32H34N6S	MH+ 535	(CDCl3): 1.94-2.02 (4H, m), 2.30 (3H, s), 2.32(3H, s), 2.65 (4H, br), 3.38 (4H, br), 3.48 (2H, t, J=6.2), 3.6 (2H, s), 4.32 (2H, t, J=5.9), 7.3 (1H, t, J=7.2), 7.38-7.43 (4H, m), 7.51-7.58 (4H, m), 8.68 (1H, s)
118	C31H35N7O2S	DCI +ve MH+ 570 (100%)	(CDCl3) 1.86-2.00 (4H,m); 2.30 (3H,s); 2.32 (3H,s); 2.57-2.70 (4H,m); 2.80-2.90 (2H,m); 3.26-3.38 (4H,m); 3.44 (2H,t,J=6.3Hz); 4.04-4.32 (5H,m); 6.80 (1H,d,J=7.5Hz); 7.29 (1H,m); 7.50 (1H,t,J=8.1Hz); 7.60 (1H,d,J=8.5Hz); 8.50 (1H,d,J=8.2Hz); 8.60 (1H,s); 8.80 (1H,m).
119	C23H26F2N6O	MH+ 441	(CDCl3): 2.00-2.15 (4H, m),2.66-2.82 (6H, m), 2.84-2.88 (2H, m), 3.48 (4H, br), 3.59 (2H, t, J=6.2), 4.43 (2H, t, J=5.9), 5.52 (1H, br. s), 6.99-7.02 (1H, m), 7.08-7.17 (2H, m), 8.63 (1H, s), 8.84 (1H, br. s)
120	C28H34N6S2	CI +ve +LMR MH+ 519.3	(CDCl3) 2.0-2.16 (4H,m); 2.45 (3H,s); 2.46 (3H,s); 2.55 (3H,s); 2.7-2.85 (6H,m); 2.83-2.92 (2H,m); 3.4-3.55 (4H,(broad)); 3.6 (2H, t, J=5.82Hz); 4.42 (2H, t, J=5.82Hz); 7.18-7.32 (4H,m); 8.75 (1H,s);
121	C32H36F2N6O3	MH+ 591	(CDCl3): 1.95-2.01 (4H, m), 2.60-2.72 (6H, m), 2.78-2.82 (2H, m), 3.36 (4H, br), 3.55 (2H, t, J=6.3), 3.83 (3H, s), 3.90 (3H, s), 4.30 (2H, t, J=5.8), 4.72 (2H, d, J=6.0), 6.80 (1H, d, J=6.0), 6.84-6.86 (1H, m), 6.98-7.10 (4H, m), 8.50 (1H, s), 9.35 (1H, t)
122	C31H34F2N6O2	MH+ 561	(CDCl3): 1.96-2.00 (4H, m), 2.55-2.70 (6H, m), 2.73-2.78 (2H, m), 3.34 (4H, br), 3.48 (2H, t, J=6.4), 3.71 (3H, s), 4.28 (2H, t, J=5.8), 4.62 (2H, d, J=5.8), 6.80 (2H, d, J=8.7), 6.85-6.88 (1H, m), 6.95-7.05 (2H, m), 7.28 (2H, d, J=8.7), 8.45 (1H, s), 9.26 (1H, t)
123	C27H32ClN7O2S	DCI +ve MH+ 518	(d6-dmso) 2.06-2.14 (4H,m); 2.50 (3H,s); 2.54 (3H,s); 3.40-3.88 (12H,m); 4.16 (2H,m); 4.58 (2H,m); 7.77

		(100%) - free base	(2H,d,J=8.5Hz); 8.40 (2H,d,J=8.4Hz); 8.80 (1H,s); 11.68 (1H, broad peak).
124	C30H30F2N6	DCI +ve MH+ 513 (100%)	(CDCl3) 2.00-2.18 (4H, m); 2.62-2.90 (11H, m); 3.26 (2H, t, J=6.2Hz); 3.48 (4H, m); 4.42 (2H, t, J=5.4Hz); 6.90-7.40 (6H, m); 8.03 (1H, m).
125	C26H27F2N7	MH+ 476	(CDCl3): 1.80-1.96 (4H, m), 2.46-2.62 (6H, m), 2.65-2.72 (2H, m), 3.23-3.30 (4H, br), 3.38 (2H, t, J=6.6), 4.27 (2H, t, J=5.5), 6.74-6.80 (1H, m), 6.85-6.98 (3H, m), 8.62 (1H, s), 8.70 (2H, d, J=4.8)
126	C32H34N6OS	DCI MH+ 551 (100%)	(CDCl3) 2.01-2.10 (4H, m); 2.31 (3H, s), 2.33 (3H, s), 2.62-2.64 (4H, m); 3.31-3.35 (4H, m); 3.45 (2H, t); 3.50 (2H, s), 4.34 (2H, t); 6.80-7.03 (6H, m), 7.20-7.31 (3H, m), 8.72 (1H, s)
127	C31H39N7O2S2	MH+ 606	(CDCl3): 1.78-1.85 (4H, m), 1.98-2.12 (4H, m), 2.40 (3H, s), 2.43 (3H, s), 2.70-2.82 (6H, m), 2.95-3.01 (2H, m), 3.26-3.32 (4H, m), 3.42-3.50 (4H, m), 3.58-3.62 (2H, m), 4.37-4.42 (2H, m), 7.40 (2H, d, J=8.2), 7.82 (2H, d, J=8.2), 8.76 (1H, s)
128	C23H25N5O	DCI MH+ 388 (100%)	(CDCL3) 1.52-1.62 (2H, m), 2.00-2.12 (7H, m), 3.05 (2H, t), 3.20 (2H, t), 3.74 (2H, d), 3.91 (2H, d), 4.38 (2H, t), 6.90-6.97 (3H, m), 7.28-7.31 (2H, m), 8.63 (1H, s).
129	C28H30N6S	CI +ve +LMR MH+ 483.1	(CDCl3) 2.0-2.16 (4H, m); 2.45 (3H, s); 2.46 (3H, s); 2.83-2.92 (4H, m); 3.4-3.55 (4H, broad); 3.6 (2H, t, J=5.82Hz); 3.7 (2H, s) 4.42 (2H, t, J=5.82Hz); 7.29-7.33 (3H, m); 7.37-7.47 (2H, m); 8.75 (1H, s)
130	C25H33N7O2S	DCI MH+ 496 (100%)	(CDCl3) 2.01-2.10 (4H, m); 2.41 (3H, s), 2.43 (3H, s), 2.82-2.84 (4H, m); 3.30 (2H, s), 3.41-3.45 (4H, m); 3.55 (2H, t); 3.60-3.70 (8H, m), 4.34 (2H, t); 8.72 (1H, s)
131	C24H34N6S	CI +ve +LMR MH+ 439.3	(CDCl3) 0.85-0.95 (3H, m); 1.24-1.37 (4H, m); 1.48-1.57 (2H, m); 1.94-2.07 (4H, m); 2.32-2.43 (8H, m); 2.57-2.7 (4H, m); 3.35-3.45 (4H, m) ; 3.48-3.55 (2H, m), 4.29-4.37 (2H, m); 8.68 (1H, m)
132	C23H25F2N5O2	M+. 441 (zwitter-ion)	(CDCl3): 1.88-2.00 (4H, m), 2.45-2.55 (6H, m), 2.67 (2H, t, J=7.2), 3.12 (2H, m), 3.55-3.70 (4H, br. m), 4.30-4.33 (2H, m), 5.10-5.22 (1H, br, NH+), 6.80-6.85 (1H, m), 6.90-7.02 (2H, m), 8.11 (1H, s)
133	C21H27N7OS	M+H = 426.3	(CDCl3); 1.9-2.0 (4H, m, 2xCH2), 2.31 (3H, s, CH3), 2.33 (3H, s, CH3), 2.7-2.8 (4H, m, 2xCH2), 3.07 (2H, s, CH2), 3.3-3.4 (4H, m, 2xCH2). 3.48 (2H, t J = 6.4 Hz, CH2), 4.30 (2H, t J =5.4 Hz, CH2), 5.40 (1H, sbr, NH), 6.97 (1H, sbr, NH), 8.65 (1H, s, ArH).
134	C24H33N7OS	M+H 468.4	(CDCl3): 1.10 (6H, d J = 6.5 Hz, 2xCH3), 1.9-2.1 (4H, m, 2xCH2), 2.31 (3H, s, CH3), 2.33 (3H, s, CH3), 2.6-2.7 (4H, m, 2xCH2), 3.02 (2H, s, CH2),

			3.3-3.4 (4H, m, 2xCH2), 3.46 (2H, t J = 6.4 Hz, CH2), 4.06 (1H, m J = 6.5Hz, CH) , 4.3 (2H, t J = 5.4 Hz), 6.9 (1H, sbr, NH), 6.66 (1H, s, ArH).
135	C22H26F2N6O	DCI +ve MH+ 429 (100%)	(CDCl3) 1.30 (3H, t, J=7.4Hz); 2.58-2.82 (8H, m); 3.30-3.45 (6H, m); 3.92 (3H, s); 5.46 (1H, broad s); 6.90 (1H, m); 7.02 (2H, m); 8.52 (1H, s); 8.90 (1H, broad s).
136	C30H37N7O2S	M+H 560.3	(CDCl3): 2.0-2.1 (4H, m, 2xCH2), 2.31 (3H, s, CH3), 2.43 (3H, s, CH3), 2.7-2.7 (4H, m, 2xCH2), 3.03 (3H, s, NCH3), 3.14 (3H, s, NCH3), 3.3-3.4 (4H, m, 2x, CH2), 3.5-3.6 (4H, m, 2xCH2), 4.4 (2H, m, CH2), 4.73 (2H, s, CH2), 6.97 (2H, d J = 8.4 Hz, 2xArH), 7.33 (2H, d J = 8.4 Hz, 2xArH), 8./74 (1H, s, ArH).
137	C29H31N7S2	CI +ve +LMR MH+ 542.3	(CDCl3) 1.93-2.08 (4H, m); 2.35 (3H, s); 2.37 (3H, s); 2.68-2.77 (4H, (broad)); 3.38 (4H,(broad)); 3.47-3.56 (2H, t, J=6.4Hz); 3.86 (2H,s); 4.3-4.39 (2H, t, J=5.93Hz); 6.95 (1H, d, J=3.45Hz); 7.1-7.18 (1H, m), 7.45 (1H, d, J=3.96); 7.6-7.71 (2H, m); 8.56 (1H, d, J=3.45Hz); 8.7 (1H, s)
138	C27H29N7S2	CI +ve +LMR MH+ 516.3	(CDCl3) 1.93-2.08 (4H, m); 2.35 (3H, s); 2.37 (3H, s); 2.68-2.77 (4H, (broad)); 3.38 (4H, (broad)); 3.47-3.56 (2H, t, J=6.4Hz); 4.03 (2H, s); 4.3-4.39 (2H, t, J=5.93Hz); 7.38 (1H, t, J=7.39Hz); 7.47 (1H, t, J=7.39); 7.88 (1H, d, J=8.39Hz), 7.9 (1H, d, J=8.39Hz); 8.72 (1H, s)
139	C29H31F2N7O	MH+ 532.5	(CDCl3): 1.85-1.95 (4H, m), 2.42 (3H, s), 2.52-2.63 (6H, m), 2.68-2.72 (2H, m), 3.30-3.35 (4H, m), 3.45 (2H, t, J=6.2), 4.25 (2H, t, J=5.0), 6.78-6.82 (1H, m), 6.87-6.98 (2H, m), 7.01 (1H, d, J=8.4), 8.06 (1H, d, J=8.4), 8.50 (1H, s), 8.60 (1H, s), 11.00 (1H, br. s)
140	C29H31N7S	CI +ve +LMR MH+ 510.3	(CDCl3) 1.93-2.08 (4H, m); 2.35 (3H, s); 2.37 (3H, s); 2.68-2.77 (4H, (broad)); 3.38 (4H, (broad)); 3.47-3.56 (2H, t, J=6.4Hz); 3.76 (2H, s); 4.3-4.39 (2H, t, J=5.93Hz); 7.55 (1H, t, J=6.89Hz), 7.7 (1H, t, J=8.36); 7.83 (1H, t, J=8.36), 7.82 (2H, d, J=8.37Hz), 8.73 (1H, s); 8.92 (1H, s)
141	C30H37N7O4S	DCI MH+ 592 (100%)	CDCL3/ 1.90-2.00 (4H, m), 2.30 (3H, s), 2.33 (3H, s), 2.72-2.74 (4H, m), 3.20 (2H, s), 3.30-3.35 (4H, m), 3.42 (2H, t), 3.70 (3H, s), 3.77 (6H, s), 4.29 (2H, t), 6.80 (2H, s), 8.68 (1H, s), 8.80 (1H, s)
142	C27H30N8O3S	DCI MH+ 547 (100%)	(CDCL3) 1.90-2.00 (4H, m), 2.30 (3H, s), 2.33 (3H, s), 2.72-2.74 (4H, m), 3.20 (2H, s), 3.30-3.35 (4H, m), 3.42 (2H, t), 4.29 (2H, t), 7.40-7.42 (1H, m), 7.92-7.94 (2H, m), 8.30 (1H, s), 8.68 (1H, s), 9.30 (1H, s)
143	C29H31F2N7O	MH+ 532	(CDCl3): 1.88-2.00 (4H, m), 2.56-2.68 (6H, m), 2.70-2.76 (2H, m), 3.32-3.38 (4H, m), 3.48 (2H, t, J=6.4),

			4.30 (2H, t, J=6.0), 4.66 (2H, d, J=6.0), 6.82-6.89 (1H, m), 6.95-7.05 (2H, m), 7.17-7.21 (1H, m), 7.66-7.70 (1H, m), 8.42-8.45 (1H, m), 8.45 (1H, s), 8.60 (1H, s), 9.40 (1H, t, CONH)
144	C31H34F2N6O	MH+ 545	(CDCl3): 1.45-1.60 (4H, m), 2.16-2.28 (6H, m), 2.30-2.38 (2H, m), 2.48 (2H, t, J=7.9), 2.90-3.00 (4H, m), 2.87 (2H, t, J=6.9), 3.24-3.32 (2H, m), 3.88 (2H, t, J=5.9), 6.44-6.50 (1H, m), 6.55-6.64 (2H, m), 6.72-6.79 (1H, m), 6.85-6.88 (4H, m), 8.02 (1H, s), 8.60 (1H, t, CONH)
145	C29H31F2N7O	MH+ 532	(CDCl3): 1.88-2.00 (4H, m), 2.08-2.17 (6H, m), 2.20-2.26 (2H,m), 3.32-3.38 (4H, m), 3.48 (2H, t, J=6.4), 4.28 (2H, t, J=6.0), 4.78 (2H, d, J=5.9), 6.82-6.86 (1H, m), 6.93-7.04 (2H, m), 7.10 (1H, t, J=7.6), 7.30 (1H, d, J=7.6), 7.56 (1H, t, J=7.6), 8.50 (1H, s), 8.50-8.55 (1H, d, J=7.6), 9.56 (1H, t, CONH)
146	C24H29N9OS	M+H 492.3	(CDCl3): 1.9-2.0 (4H, m, 2xCH2), 2.30 (3H, s, CH3), 2.32 (3H, s, CH3), 2.7-2.8 (4H, m), 3.19 (2H, s, CH2), 3.3-3.4 (4H, m), 3.46 (2H, t J = 6.6 Hz, CH2), 4.31 (2H, t J = 5.2 Hz, CH2) 6.58)1H, sbr, NH), 7.43 (1H, S, ArH), 8.65 (1H, s, ArH), 9.43 (1H, s, ArH).
147	C32H39N7O3S	M+H 602.4	(CDCl3): 1.8-1.9 (4H, m, 2xCH2), 2.20 (3H, s, CH3), 2.23 (3H, s, CH3), 2.4-2.5 (4H, m, 2xCH2), 3.1-3.2 (4H, m 2xCH2), 3.3-3.4 (4H, m, 2xCH2), 3.4-3.5 (6H, m, 3xCH2), 4.17 (2H, t J = 5.6 Hz, CH2), 4.53 (2H, s, CH2), 6.76 (2H, d J = 8.6 Hz, 2xArH, 7.13 (2H, d J= 8.6 Hz, 2xArH), 8.53 (1H, s, ArH)
148	C32H37F2N7O	MH+ 574 (~30%)	(CDCl3): 1.92-2.02 (4H, m), 2.61-2.72 (6H, m), 2.75-2.79 (2H, m), 2.90 (6H, s), 3.32-3.38 (4H, m), 3.54 (2H, t, J=6.5), 4.32 (2H, t, J=6.0), 4.61 (2H, d, J=5.7), 6.70 (2H, d, J=8.7), 6.90-6.94 (1H, m), 7.02-7.12 (2H, m), 7.30 (2H, d, J=8.7), 8.50 (1H, s), 9.21 (1H, t, NH)
149	C34H39F2N7O	MH+ 600	(CDCl3): 1.88-2.00 (8H, m), 2.54-2.68 (6H, m), 2.74-2.80 (2H, m), 3.19-3.24 (4H, m), 3.35-3.40 (4H, m), 3.55 (2H, t, J=6.5), 4.30 (2H, t, J=5.9), 4.70 (2H, d, J=5.8), 6.85-6.90 (2H, m), 6.98-7.08 (3H, m), 7.18 (1H, t), 7.32 (1H, d), 8.42 (1H, s), 9.40 (1H, t, NH)
150	C28H36F2N6O	MH+ 511	(CDCl3): 1.02 (9H, s), 1.90-2.02 (4H, m), 2.62-2.74 (6H, m), 2.79-2.83 (2H, m), 3.30 (2H, d, J=6.1), 3.35-3.42 (4H, m), 3.55 (2H, t, J=6.4), 4.33 (2H, t, J=5.4), 6.88-6.92 (1H, m), 7.00-7.10 (2H, m), 8.54 (1H, s), 9.10 (1H, t, CONH)
151	C34H39F2N7O 2	MH+ 616	(CDCl3): 1.86-1.94 (4H, m), 2.54-2.70 (6H, m), 2,73-2.80 (2H, m), 2.84-2.89 (4H, m), 3.42 (2H, t, J=6.5), 3.75-3.80 (4H, m), 4.22 (2H, t, J=5.5), 4.65 (2H, d, J=5.8), 6.78-6.82 (1H, m), 6.88-7.00 (3H, m), 7.04

			(1H, d, J=7.8), 7.15 (1H, t, J=7.5), 7.30 (1H, d, J=7.5), 8.32 (1H, s), 9.25 (1H, t, CONH)
152	C32H36F2N6O3	MH+ 591	(CDCl3): 1.98-2.10 (4H, m), 2.69-2.80 (6H, m), 2.85-2.90 (2H, m), 3.42-3.48 (4H, m), 3.63 (2H, t, J=5.6), 3.85 (3H, s), 3.96 (3H, s), 4.40 (2H, t, J=5.8), 4.70 (2H, d, J=5.8), 6.50 (1H, d, J=8.3), 6.54 (1H, s), 6.95-7.02 (1H, m), 7.10-7.18 (2H, m), 7.35 (1H, d, J=8.3), 8.58 (1H, s), 9.46 (1H, t, J=5.8, CONH)
153	C35H42F2N8O	MH+ 629	(CDCl3): 1.88-2.00 (4H, m), 2.30 (3H, s), 2.55-2.68 (10H, m), 2.70-2.75 (2H, m), 2.95 (4H, t, J=4.7), 3.30-3.34 (4H, m), 3.52 (2H, t, J=6.5), 4.28 (2H, t, J=5.5), 4.72 (2H, d, J=5.9), 6.85-6.90 (1H, m), 6.94-7.02 (3H, m), 7.02 (1H, d, J=6.9), 7.10-7.15 (1H, m), 7.34 (1H, d, J=7.5), 8.38 (1H, s), 9.26 (1H, t, CONH)
154	C29H29F2N7S	CI +ve +LMR MH+ 546.3	(CDCl3) 1.93-2.08 (4H, m); 2.35 (3H, s); 2.37 (3H, s); 2.68-2.77 (4H, (broad)); 3.38 (4H, (broad)); 3.47-3.56 (2H, t, J=6.4Hz); 3.76 (2H, s); 4.3-4.39 (2H, t, J=5.93Hz); 7.54 (1H, t, J=9.34Hz); 7.7 (1H, d, J=8.37Hz); 7.85 (1H, t, J=9.59Hz); 8.7 (1H, d, J=8.37Hz); 8.7 (1H, s)
155	C31H32F2N6O3	MH+ 575	(CDCl3): 1.88-2.00 (4H, m), 2.55-2.68 (6H, m), 2.70-2.78 (2H, m), 3.30-3.35 (4H, m), 3.52 (2H, t, J=6.5), 4.28 (2H, t, J=6.0), 4.60 (2H, d, J=5.9), 6.65 (1H, d, J=7.8), 6.72 (1H, t, J=7.8), 6.84-6.88 (2H, m), 6.95-7.03 (2H, m), 8.45 (1H, s), 9.30 (1H, t, CONH)
156	C27H34F2N6O	MH+ 497	(CDCl3): 1.00 (6H, d, J=6.7), 1.90-2.05 (5H, m), 2.63-2.72 (6H, m), 2.78-2.82 (2H, m), 3.30 (2H, t, J=6.3), 3.35-3.41 (4H, m), 3.54 (2H, t, J=6.5), 4.33 (2H, t, J=6.0), 6.88-6.92 (1H, m), 7.00-7.10 (2H, m), 8.54 (1H, s), 9.04 (1H, t, CONH)
157	C33H33F2N7O	MH+ 582	(CDCl3): 1.88-2.00 (4H, m), 2.55-2.69 (6H, m), 2.70-2.76 (2H, m), 3.33-3.38 (4H, m), 3.53 (2H, t, J=6.5), 4.30 (2H, t, J=5.6), 4.96 (2H, d, J=5.7), 6.82-6.88 (1H, m), 6.92-7.03 (2H, m), 7.40-7.46 (2H, m), 7.64 (1H, t, J=7.1), 7.71 (1H, d, J=8.1), 8.02 (2H, d, J=8.4), 8.51 (1H, s), 9.80 (1H, t, CONH)
158	C33H33F2N7O	MH+ 582	(CDCl3): 1.80-1.92 (4H, m), 2.45-2.57 (6H, m), 2.60-2.64 (2H, m), 3.20-3.24 (4H, m), 3.38 (2H, t, J=6.5), 4.18 (2H, t, J=5.6), 5.02 (2H, d, J=6.0), 6.72-6.78 (1H, m), 6.80-6.95 (2H, m), 7.30 (1H, d, J=4.4), 7.43 (1H, t, J=7.2), 7.54 (1H, t, J=7.2), 7.94-8.00 (2H, m), 8.32 (1H, s), 8.68 (1H, d, J=4.4), 9.40 (1H, t, J=6.0)
159	C29H29F2N7O3	MH+ 562	(CDCl3): 2.06-2.18 (4H, m), 2.73-2.83 (6H, m), 2.35-2.92 (2H, m), 3.50-3.58 (4H, m), 3.68 (2H, t, J=6.2), 4.48 (2H, t, J=4.6), 6.98-7.03 (1H, m), 7.10-7.18 (2H, m), 7.58 (1H, t, J=8.2), 8.00 (1H, d, J=7.9), 8.22 (1H,

			d, J=7.9), 8.72 (1H, s), 8.80 (1H, s)
160	C32H36F2N6O3	MH+ 591	(CDCl3): 1.9-2.02 (4H, m), 2.55-2.67 (6H, m), 2.72-2.78 (2H, m), 3.35-3.40 (4H, m), 3.50 (2H, t, J=6.5), 3.75 (6H, s), 4.30 (2H, t, J=5.8), 4.73 (2H, d, J=5.6), 6.52 (2H, d, J=8.3), 6.88-6.95 (1H, m), 6.95-7.08 (2H, m), 7.18 (1H, t, J=8.3), 8.48 (1H, s), 9.40 (1H, t, NH)
161	C30H32F2N6O2	MH+ 547	(CDCl3): 1.90-2.02 (4H, m), 2.58-2.68 (6H, m), 2.71-2.78 (2H, m), 3.35-3.40 (4H, m), 3.55 (2H, t, J=6.4), 3.80 (3H, s), 4.32 (2H, t, J=4.8), 6.58 (1H, d, J=7.4), 6.84-6.90 (1H, m), 6.92-7.05 (3H, m), 7.20 (1H, m), 7.52 (1H, s), 8.55 (1H, s), 11.07 (1H, br.s, CONH)
162	C28H29F2N7O	MH+ 518	(CDCl3): 1.90-2.03 (4H, m), 2.60-2.71 (6H, m), 2.72-2.78 (2H, m), 3.38-3.43 (4H,m), 3.55 (2H, t, J=6.2), 4.32 (2H, t, J=6.0), 6.82-6.88 (1H, m), 6.95-7.04 (2H, m), 7.22-7.25 (1H, m), 8.23-8.28 (2H, m), 8.55 (1H, s), 8.80 (1H, s)
163	C29H30F2N6O	MH+ 517	(CDCl3): 2.00-2.10 (4H, m), 2.68-2.78 (6H, m), 2.82-2.88 (2H, m), 3.44-3.49 (4H, m), 3.63 (2H, t, J=6.4), 4.40 (2H, t, J=4.5), 6.90-6.98 (1H, m), 7.02-7.13 (3H, m), 7.38 (2H, t, J=8.3), 7.82 (2H, d, J=7.7), 8.63 (1H, s), 11.12 (1H, br, NH)
164	C28H29F2N7O	MH+ 518	(CDCl3): 2.15-2.25 (4H, m), 2.85-2.95 (6H, m), 2.98-3.04 (2H, m), 3.61-3.68 (4H, m), 3.80 (2H, t, J=6.4), 4.60 (2H, t, J=5.8), 7.08-7.13 (1H, m), 7.18-7.32 (4H, m), 7.90 (1H, t, J=7.1), 8.60 (1H, d, J=7.9), 8.92 (1H, s), 11.85 (1H, br, NH)
165	C28H29F2N7O	MH+ 518	(CDCl3): 1.82-1.92 (4H, m), 2.48-2.58 (6H, m), 2.62-2.68 (2H, m), 3.28-3.32 (4H, m), 3.40 (2H, t, J=6.2), 4.22 (2H, t, J=5.3), 6.75-6.80 (1H, m), 6.85-6.94 (2H, m), 7.55 (2H, d, J=6.3), 8.32 (2H, d, J=6.3), 8.45 (1H, s), 11.20 (1H, br, NH)
166	C31H35F2N7O	MH+ 560	(CDCl3): 1.95-2.08 (4H, m), 2.65-2.75 (6H, m), 2.78-2.83 (2H, m), 3.00 (6H, s,), 3.40-3.45 (4H, m), 3.60-3.64 (2H, m), 4.35-4.40 (2H, m), 6.48 (1H, d, J=7.3), 6.90-6.95 (1H, m), 7.02-7.10 (3H, m), 7.20 (1H, t, J=7.0), 7.40 (1H, s), 8.52 (1H, s), 11.05 (1H, br, NH)
167	C26H29N7	MH+ 440	(CDCl3): 2.05-2.20 (4H, m), 2.78-2.90 (6H, m), 2.93-2.98 (2H, m), 3.50 (4H, br. m), 3.60 (2H, t, J=6.7), 4.50 (2H, t, J=5.8), 7.15 (1H, t, J=4.8), 7.28-7.40 (5H, m), 8.88 (1H, s), 8.95 (2H, d, J=4.8)
168	C25H30F2N6O	MH+ 469	(CDCl3): 1.44 (3H, t, J=7.2), 2.08-2.18 (4H, m), 2.77-2.90 (6H, m), 2.92-2.98 (2H, m), 3.52-3.60 (4H, m), 3.65-3.73 (4H, m), 4.50 (2H, t, J=6.0), 7.02-7.08 (1H, m), 7.14-7.28 (2H, m), 8.70 (1H, s), 9.05 (1H, br, NH)
169	C21H22F2N6	DCI +ve MH+ 397	(CDCl3) 2.55 (3H, s); 2.56-2.78 (8H, m); 3.36 (4H, m); 3.87 (3H, s); 6.85 (1H, m); 7.00 (2H, m); 8.56

		(100%)	(1H, s).
170	C24H26F2N6	DCI +ve MH+ 437 (100%)	(CDCl3) 1.78-2.10 (6H, m); 2.60-2.95 (8H, m); 3.24 (2H, m); 3.50 (4H, m); 4.58 (2H, m); 7.00 (1H, m); 7.14 (2H, m); 8.72 (1H, s).
171	C24H28F2N6O	DCI +ve MH+ 455 (100%)	(d6-dmso) 1.5-1.75 (6H, m); 2.42-2.58 (6H, m); 2.64 (2H, t, J=7.5Hz); 3.10-3.22 (4H, m); 3.49 (2H, m); 3.32 (2H, m); 6.97 (1H, m); 7.14 (1H, broad s); 7.20 (2H, m); 8.34 (1H, s); 8.40 (1H, broad s).
172	C21H24F2N6O	DCI +ve MH+ 415 (100%)	(CDCl3) 2.52-2.70 (6H, m); 2.74 (2H, t, J=7.7Hz); 2.80 (3H, s); 3.34 (4H, m); 3.85 (3H, s); 5.45 (1H, br, s); 6.86 (1H, m); 7.00 (2H, m); 8.50 (1H, s); 8.85 (1H, br, s).
173	C22H24F2N6O	DCI/NH3 MH+ 427 (100%)	(CDCL3) 2.51-2.68 (8H, m), 2.75 (2H, t), 3.35 (2H, t), 3.48-3.52 (4H, m), 4.25 (2H, t), 5.45 (1H, s), 6.84-6.88 (1H, m), 6.92-7.04 (2H, m), 8.45 (1H, s), 8.47 (1H, s)
174	C26H32F2N6O	MH+ 483	(CDCl3): 1.08 (3H, t, J=7.4), 1.70-1.78 (2H, m), 2.00-2.12 (4H, m), 2.68-2.80 (6H, m), 2.82-2.86 (2H, m), 3.42-3.53 (6H, m), 3.62 (2H, t, J=6.5), 4.40 (2H, t, J=5.9), 6.97-7.02 (1H, m), 7.10-7.20 (2H, m), 8.60 (1H, s), 9.03 (1H, br. t, NH)
175	C29H31F2N7O	MH+ 532	(CDCl3): 2.00-2.15 (4H, m), 2.57 (3H, s), 2.70-2.82 (6H, m), 2.85-2.92 (2H, m), 3.48-3.52 (4H, m), 3.68 (2H, t, J=6.4), 4.48 (2H, t, J=6.0), 7.00-7.05 (1H, m), 7.10-7.18 (2H, m), 7.23 (1H, d, J=4.9), 8.33 (1H, d, J=4.9), 8.68 (1H, s), 9.51 (1H, s), 11.05 (1H,br,s, NH)
176	C27H28F2N8O	MH+ 519	(CDCl3): 1.94-2.03 (4H, m), 2.58-2.68 (6H, m), 2.72-2.76 (2H, m), 3.38-3.41 (4H, m), 3.52 (2H, t, J=6.3), 4.32 (2H, t, J=5.8), 6.82-6.88 (1H, m), 6.95-7.03 (2H, m), 8.55 (1H, s), 8.87 (1H, s), 9.12 (2H, s), 11.22 (1H, br)
177	C28H28BrF2N7O	MH+ 597:598 (1:1 - Br isotopes)	(CDCl3): 1.88-1.96 (4H, m), 2.50-2.63 (6H, m), 2.65-2.72 (2H, m), 3.30-3.35 (4H, m), 3.45 (2H, t, J=6.9), 4.26 (2H, t, J=5.3), 6.78-6.83 (1H, m), 6.90-7.00 (2H, m), 8.21 (1H, s), 8.51 (1H, s), 8.53 (1H, s), 8.60 (1H, s), 11.20 (1H, br, NH)
178	C30H33F2N7O2	MH+ 562	(CDCl3): 2.00-2.15 (4H, m), 2.70-2.82 (6H, m), 2.85-2.91 (2H, m), 3.48-3.52 (4H, m), 3.65 (2H, t, J=6.5), 4.00 (3H, s), 4.40 (2H, t, J=5.4), 4.71 (2H, d, J=5.9), 6.80 (1H, d, J=8.6), 6.95-7.02 (1H, m), 7.08-7.18 (2H, m), 7.72 (1H, dd), 8.28 (1H, d, J=2.2), 8.60 (1H, s), 9.40 (1H, t, NH)
179	C29H31F2N7O2	MH+ 548	(CDCl3): 1.92-2.03 (4H, m), 2.56-2.68 (6H, m), 2.72-2.76 (2H, m), 3.35-3.40 (4H, m), 3.50 (2H, t, J=6.4), 3.86 (3H, s), 4.30 (2H, t, J=5.9), 6.68 (1H, d, J=8.9), 6.82-6.88 (1H, m), 6.95-7.03 (2H, m), 8.04 (1H, d,

			J=8.9), 8.36 (1H, s), 8.54 (1H, s), 10.90 (1H, br, NH)
180	C32H31F2N7O	MH+ 568	(CDCl3): 2.00-2.12 (4H, m), 2.66-2.78 (6H, m), 2.80-2.86 (2H, m), 3.44-3.50 (4H, m), 3.68 (2H, t, J=6.4), 4.42 (2H, t, J=6.0), 6.91-6.96 (1H, m), 7.03-7.11 (2H, m), 7.65 (1H, t, J=7.3), 7.80 (1H, t, J=7.3), 8.02 (1H, d, J=8.1), 8.50 (1H, d, J=8.4), 8.72 (1H, s), 9.08 (1H, s), 9.54 (1H, s), 11.60 (1H, br)
181	C32H31F2N7O	MH+ 568	(CDCl3): 1.95-2.02 (4H, m), 2.58-2.70 (6H, m), 2.72-2.78 (2H, m), 3.38-3.45 (4H, m), 3.58 (2H, t, J=6.2), 4.35 (2H, t, J=6.0), 6.85-6.90 (1H, m), 6.95-7.02 (2H, m), 7.45 (1H, t, J=8.0), 7.53 (1H, t, J=8.0), 7.75 (1H, d, J=7.4), 8.00 (1H, d, J=7.4), 8.60 (1H, s), 8.90 (1H, s), 8.96 (1H, s), 11.42 (1H, br)
182	C32H36F2N8O	MH+ 587	(CDCl3): 1.90-2.03 (8H,m), 2.58-2.70 (6H, m), 2.72-2.78 (2H, m), 3.28-3.32 (4H, m), 3.34-2.41 (4H, m), 3.57 (2H, t, J=6.4), 4.30 (2H, t, J=6.0), 6.82-6.88 (1H, m), 6.95-702 (2H, m), 7.64 (2H, m), 8.04 (1H, s), 8.56 (1H, s), 11.05 (1H, NH)
183	C30H33F2N7O	MH+ 546	(CDCl3): 1.88-2.00 (4H, m), 2.45 (3H, s), 2.52-2.68 (6H, m), 2.68-2.72 (2H, m), 3.28-3.33 (4H, m), 3.50 (2H, t, J=6.4), 4.24 (2H, t, J=6.0), 4.58 (2H, d, J=6.0), 6.80-6.88 (1H, m), 6.90-7.04 (3H, m), 7.55 (1H, d, J=8.0), 8.40 (1H, s), 8.45 (1H, s), 9.30 (1H, t, NH)
184	C30H33F2N7O	MH+ 546	(CDCl3): 1.95-2.10 (4H, m), 2.62 (3H, s), 2.67-2.80 (6H, m), 2.80-2.88 (2H, m), 3.44-3.52 (4H, m), 3.62 (2H, t, J=6.4), 4.39 (2H, t, J=6.0), 4.84 (2H, d, J=5.8), 6.92-6.98 (1H, m), 7.02-7.12 (3H, m), 7.22 (1H, d, J=7.5), 7.55 (1H, t, J=7.5), 8.60 (1H, s), 9.72 (1H, t, NH)
185	C24H28F2N6O	MH+ 455	(CDCl3): 1.20 (3H, t, J=7.2), 2.50-2.68 (8H, m), 2.72-2.78 (2H, m), 3.36 (2H, t, J=7.5), 3.45-3.52 (6H, m), 4.24 (2H, t, J=7.0), 6.82-6.88 (1H, m), 6.92-7.05 (2H, m), 8.42 (1H, s), 8.52 (1H, t, NH)
186	C26H32F2N6O	DCI +ve MH+ 483 (100%)	(CDCL3) 1.13 (3H, t), 1.54-1.75 (6H, m), 2.46-2.53 (6H, m), 2.63 (2H, t), 3.20-3.26 (4H, m), 3.33-3.40 (2H, m), 3.51-3.60 (2H, m), 4.30 (2H, t), 6.70-6.74 (1H, m), 6.81-6.91 (2H, m), 8.37 (1H, s), 9.01 (1H, t).
187	C23H26F2N6	DCI +ve MH+ 425 (100%)	(CDCl3) 1.50 (6H, d); 2.54-2.70 (6H, m); 2.72 (2H, t); 3.20 (1H, septet), 3.30 (4H, m); 3.90 (3H, s); 6.80-6.84 (1H, m), 6.92-7.0 (2H, m); 8.52 (1H, s).
188	C22H24F2N6	DCI +ve MH+ 411 (100%)	(CDCl3) 1.36 (3H, t, J=7.6Hz); 2.54-2.70 (6H, m); 2.72 (2H, t, J=7.7Hz); 2.95 (2H, q, J=7.7Hz); 3.36 (4H, m); 3.90 (3H, s); 6.86 (1H, m); 7.0 (2H, m); 8.56 (1H, s).
189	C15H17N5O	ESI+ MH+, 284	(CDCl3) 2.0 (4H, m, 2xCH2), 3.15 (2H, t, CH2), 3.30 (4H, t, 2xCH2), 3.80 (4H, t, 2xCH2), 4.30 (2H, t,

			CH2), 8.58 (1H,s),.
190	C15H17N5	ESI+, MH+, 268	(CDCl3) 2.00 (8H, m, 4xCH2), 3.20 (2H, t, CH2), 3.70 (4H, t, 2xCH2), 4.35 (2h, t, CH2), 8.45 (1H, s).
191	C20H21N5	ESI+ MH+ 332	(CDCl3) 1.90 (4H, m, 2xCH2), 2.95 (2H, t, CH2), 2.98 (3H, s, CH3), 3.15 (2H, t, CH2), 3.65 (2H, t, CH2), 4.00 (2H, t, CH2), 7.10-7.25 (5H, m), 8.60 (1H,s).
192	C22H23N5O	ESI+ MH+ 374	(CDCL3) 1.95 (2H, m, CH2), 2.05 (4H, m), 2.30 (2H, m, CH2), 3.20 (2H, t, CH2), 3.60 (4H, m, 2xCH2), 4.40 (2H, t, CH2), 7.30-7.50 (5H, m,), 8.60 (1H, s),
193	C17H24N6	MH+ 313	(CDCl3): 1.79 (2H, quintet, J=7.4), 1.98-2.08 (4H, m), 2.20 (6H, s), 2.25 (2H, t, J=7.2), 2.98 (3H, s), 3.20 (2H, t, J=6.5), 3.40 (2H, t, J=7.4), 4.35 (2H, t, J=6.0), 8.55 (1H, s)
194	C15H16N6	(ESI+): MH+ 281	(CDCl3): 1.98-2.07 (2H, m), 2.07-2.15 (2H, m), 2.75 (2H, t, J=6.4), 3.05 (3H, s), 3.21 (2H, t, J=6.6), 3.68 (2H, t, J=6.4), 4.45 (2H, t, J=5.7), 8.61 (1H, s)
195	C16H19N5O2	(ESI+): MH+ 314	(DMSO-d6): 1.80 (2H, quintet, J=7.2), 1.87-2.00 (4H, m), 2.22 (2H, t, J=7.4), 2.88 (3H, s), 3.12 (2H, t, J=7.8), 3.35 (2H, t, J=7.6), 4.32 (2H, t, J=5.7), 8.40 (1H, s), 12.00 (1H, br)
196	C23H24N6O	DCI MH+ 401 (100%)	(CDCl3) 2.01-2.12 (8H, m), 2.45-2.53 (1H, m), 3.00-3.10 (2H, m), 3.21 (2H, t), 3.75 (2H, d), 4.40 (2H, t), 7.11-7.14 (1H, m), 7.23 (1H, s), 7.35 (2H, t), 7.57 (2H, d), 8.64 (1H, s)
197	C24H28N6	DCI MH+ 401 (100%)	(CDCl3) 1.80 (2H, qd), 2.01-2.11 (6H, m),2.25 (3H, s), 2.62-2.70 (1H, m), 3.00 (2H, t), 3.18 (2H, t), 3.65 (2H, s), 3.75 (2H, d), 4.37 (2H, t), 7.22-7.32 (5H, m), 8.61 (1H, s).

Example 5: Tablet composition

Tablets, each weighing 0.15 g and containing 25 mg of a compound of the invention were manufactured as follows:

Composition for 10,000 tablets

Compound of the invention (250 g)

Lactose (800 g)

Corn starch (415g)

Talc powder (30 g)
Magnesium stearate (5 g)

The compound of the invention, lactose and half of the corn starch were mixed. The mixture was then forced through a sieve 0.5 mm mesh size. Corn starch (10 g) is suspended in warm water (90 ml). The resulting paste was used to granulate the powder. The granulate was dried and broken up into small fragments on a sieve of 1.4 mm mesh size. The remaining quantity of starch, talc and magnesium was added, carefully mixed and processed into tablets.

Example 6: Injectable Formulation

Compound of the invention	200mg
Hydrochloric Acid Solution 0.1M or Sodium Hydroxide Solution 0.1M q.s. to pH	4.0 to 7.0
Sterile water q.s. to	10 ml

The compound of the invention was dissolved in most of the water (35° 40° C) and the pH adjusted to between 4.0 and 7.0 with the hydrochloric acid or the sodium hydroxide as appropriate. The batch was then made up to volume with water and filtered through a sterile micropore filter into a sterile 10 ml amber glass vial (type 1) and sealed with sterile closures and overseals.

Example 7: Intramuscular Injection

Compound of the invention	200 mg
Benzyl Alcohol	0.10 g
Glycofurol 75	1.45 g
Water for injection q.s to	3.00 ml

The compound of the invention was dissolved in the glycofurol. The benzyl alcohol was then added and dissolved, and water added to 3 ml. The mixture was then

filtered through a sterile micropore filter and sealed in sterile 3 ml glass vials (type 1).

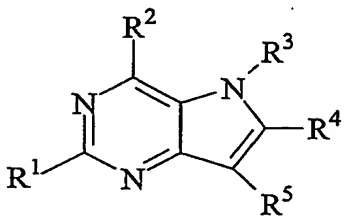
Example 8: Syrup Formulation

Compound of invention	250 mg
Sorbitol Solution	1.50 g
Glycerol	2.00 g
Sodium benzoate	0.005 g
Flavour	0.0125 ml
Purified Water q.s. to	5.00 ml

The compound of the invention was dissolved in a mixture of the glycerol and most of the purified water. An aqueous solution of the sodium benzoate was then added to the solution, followed by addition of the sorbital solution and finally the flavour. The volume was made up with purified water and mixed well.

CLAIMS

1. A compound which is a pyrrolopyrimidine of formula (I)



(I)

wherein:

R^1 is selected from R^9 and halogen;

R^2 is NR^6R^7;

R^3 is selected from H, C_1-C_6 alkyl which is unsubstituted or substituted and $-(CH_2)_nAr$;

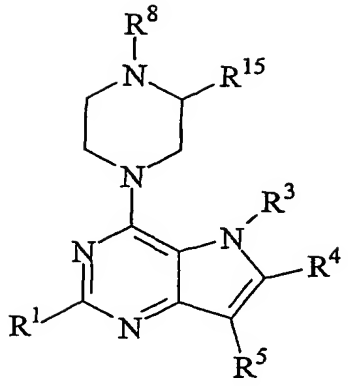
R^4 is selected from H, C_1-C_6 alkyl and $-(CH_2)_nAr$; or R^3 and R^4 form, together with the N and C atoms to which they are attached, a fused five-, six-, seven- or eight-membered N-containing saturated ring which is unsubstituted or substituted;

R^5 is selected from CN, CO_2R^9, $C(O)NR^{10}R^{11}$, $-(CH_2)_nOH$, $-(CH_2)_nNR^{10}R^{11}$, $-C\equiv CH$, $-C(S)NR^{10}R^{11}$, $-C(NH_2)=NOR^9$, $-C(R^9)=NOR^9$, $-C(NH_2)NH$, $-C(O)R^9$ and an unsaturated 5- or 6-membered heterocyclic group which contains 1, 2 or 3 heteroatoms selected from N, O and S and which is unsubstituted or substituted;

R^6 and R^7, which are the same or different, are selected from C_1-C_6 alkyl which is unsubstituted or substituted, $-(CH_2)_nX$ and $-(CH_2)_nAr$; or R^6 and R^7 form, together with the nitrogen atom to which they are attached, a saturated five-, six-, seven- or eight-membered heterocyclic group which contains one nitrogen atom and 0 or from 1 to 3 additional heteroatoms selected from N, O and S, which is unsubstituted or substituted and which optionally contains one or two bridgehead atoms;

R^{10} and R^{11}, which are the same or different, are selected from H, C_1-C_6 alkyl which is unsubstituted or substituted, -$(CH_2)_nC_3$-C_{10} cycloalkyl and -$(CH_2)_nAr$; or R^{10} and R^{11} form, together with the nitrogen atom to which they are attached, a saturated five or six membered heterocyclic group which contains a nitrogen atom and 0 or from 1 to 3 additional heteroatoms selected from O, S and N, which is unsubstituted or substituted and which is optionally fused to a benzene ring which is unsubstituted or substituted;
n is the same or different when more than one is present within a given substituent group and is 0 or an integer from 1 to 6;
X is selected from -CN, -CO_2R^9 and -$NR^{10}R^{11}$;
R^9 is the same or different when more than one is present within a given substituent group and is selected from -H, -QAr, -$(CH_2)_nAr$, C_1-C_6 alkyl which is unsubstituted or substituted and -$(CH_2)_nC_3$-C_{10}cycloalkyl, wherein the cycloalkyl moiety is optionally fused to a benzene ring which is unsubstituted or substituted;
Q is C_2-C_6 alkenylene or C_2-C_6 alkynylene; and
Ar is an unsaturated C_6-C_{10} membered carbocyclic group or an unsaturated 5-11 membered heterocyclic group, which groups are unsubstituted or substituted;
or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein the pyrrolopyrimidine is of formula (Ia)



(Ia)

wherein:

R^1, R^3, R^4 and R^5 are as defined in claim 1;

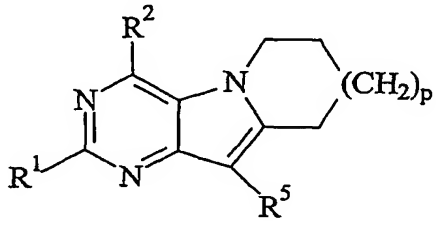
R^8 is selected from -H, -$(alk)_nY$, -$(alk)_nC(O)Y$, -$C(O)(alk)_nY$, -$C(O)NH(alk)_nY$, -$alk)_nCHOH(alk)_nOY$, -$(alk)_nC{\equiv}CY$, -$(alk)_nOY$, -$S(O)_m(alk)_nY$ and -$(alk)_nC(O)NR^{10}R^{11}$ wherein m is 0, 1 or 2 and alk is C_1-C_6 alkylene which is unsubstituted or substituted by Y;

n, Q, R^{10} and R^{11} are as defined in claim 1;

Y is selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, $NR^{10}R^{11}$ and Ar; and

R^{15} is H or C_1-C_6 alkyl.

3. A compound according to claim 1 wherein the pyrrolopyrimidine is of formula (Ib):



(Ib)

wherein R^1, R^2 and R^5 are as defined in claim 1 and p is 1,2 or 3.

4. A compound selected from:

4-(4-Phenyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

4-(4-Methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

4-(4-Pyrimidin-2-yl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

4-[4-(2-Hydroxy-ethyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

4-(4-Benzyl-piperazin-1-yl)-6,7,8,9-tetrahydro-5H-1,3,4b-triaza-benzo[a]azulene-10-carbonitrile

4-(4-Phenethyl-piperazine-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

2-(9-Cyano-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-ylamino)-N,N-diethyl-4-methoxy-benzenesulfonamide

4-(4-Phenethyl-piperazin-1-yl)-5H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile

1-[4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-9-yl]-ethanone

Cyclopentyl-[4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-9-yl]-methanone

4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbothioic acid amide

9-(4-Methyl-thiazol-2-yl)-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

4-Piperazin-1-yl-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

4-[4-(3-Phenyl-propyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

4-(4-Phenylacetyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

5-Methyl-4-(4-phenethyl-piperazin-1-yl)-5H-pyrrolo[3,2,d]pyrimidine-7-carbonitrile

3-Methyl-1-[4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-9-yl]-butan-1-one

4-{4-[2-(1H-Indol-3-yl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

4-(4-Diphenylacetyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

4-[4-(2-Oxo-2-phenyl-ethyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

4-(4-Phenylmethanesulfonyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

4-(4-Phenethyl-piperazin-1-yl)-9-(4-phenyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

9-(4-tert-Butyl-thiazol-2-yl)-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

5-Ethyl-4-(4-phenethyl-piperazin-1-yl)-5H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile

4-(4-Phenethyl-piperazin-1-yl)-9-(4-trifluoromethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

9-(4,5-Dimethyl-thiazol-2-yl)-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

5-Phenethyl-4-(4-phenethyl-piperazin-1-yl)-5H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile

2-[4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-9-yl]-thiazole-4-carboxylic acid; hydrobromide

[4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-9-yl]-phenyl-methanone

4-{4-[2-(4-Nitro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

4-{4-[2-(4-Methoxy-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

4-[4-(2-Cyclohexyl-ethyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

4-(4-Phenethyl-piperazin-1-yl)-9-thiazol-2-yl-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

4-[4-(2-Naphthalen-1-yl-ethyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

4-(3-Methyl-4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

4-{4-[2-(3-Trifluoromethyl-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

4-{4-[2-(3-Chloro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

4-{4-[2-(3-Nitro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

4-[4-(2-o-Tolyl-ethyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

4-{4-[2-(2-Fluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

4-[4-(2-Piperidin-1-yl-ethyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

4-{4-[2-(4-Hydroxy-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

9-Ethynyl-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

5,6-Dimethyl-4-(4-phenethyl-piperazin-1-yl)-5H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile

4-[4-(2-Phenyl-propyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

[4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-9-yl]-methanol

4-(4-Phenethyl-piperazin-1-yl)-9-piperidin-1-ylmethyl-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

4-{4-[2-(4-Cyano-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

2-Iodo-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

N-Hydroxy-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxamidine

2-[4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-9-yl]-

thiazole-4-carboxylic acid ethyl ester

4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid amide

6-Benzyl-4-{4-[2-(3,4-difluoro-phenyl)-ethyl]-piperazin-1-yl}-5-methyl-5H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile

4-(4-Indan-2-yl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

4-(4-Phenethyl-piperazin-1-yl)-2-phenyl-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

4-{2-[4-(9-Cyano-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl)-piperazin-1-yl]-ethyl}-benzoic acid; hydrochloride

4-{4-[2-(3,4,5-Trimethoxy-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

9-(5-Methyl-1H-[1,2,4]triazol-3-yl)-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

4-{4-[2-(3-Amino-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

3-(2-{4-[9-(4,5-Dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl]-piperazin-1-yl}-ethyl)-benzoic acid methyl ester

9-(4,5-Dimethyl-thiazol-2-yl)-4-{4-[2-(3-nitro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

2-(3-Methoxy-phenyl)-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

2-(4-Nitro-phenyl)-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

4-{4-[2-(3,5-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

4-{4-[2-(2,3-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

4-{4-[2-(2,4-Dichloro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-

fluorene-9-carbonitrile

2-(4-Amino-phenyl)-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

N-{4-[9-Cyano-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-2-yl]-phenyl}-acetamide

N-{4-[9-Cyano-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-2-yl]-phenyl}-benzamide

N-{4-[9-Cyano-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-2-yl]-phenyl}-isonicotinamide

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-9-(4,5-dihydro-1H-imidazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-6-isopropyl-5-methyl-5H-pyrrolo[3,2-d]pyrimidine-7-carboxylic acid amide

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-9-(4,5-dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

N-(3-{2-[4-(9-Cyano-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl)-piperazin-1-yl]-ethyl}-phenyl)-acetamide

N-(3-{2-[4-(9-Cyano-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl)-piperazin-1-yl]-ethyl}-phenyl)-methane sulfonamide

9-(5-Methyl-thiazol-2-yl)-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

9-(5-Methyl-[1,2,4]oxadiazol-3-yl)-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

9-(4,5-Dimethyl-thiazol-2-yl)-4-[4-(2-pyridin-4-yl-ethyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid ethylamide

4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbothioic acid ethylamide

4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid benzylamide

4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (pyridin-3-ylmethyl)-amide

4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid cyclohexylmethyl-amide

9-(4,5-Dimethyl-1H-imidazol-2-yl)-4-(4-phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

Bis-Hydrochloride salt of 4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-2-pyridin-4-yl-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

1-[4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-9-yl]-ethanone O-methyl-oxime

1-[4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-9-yl]-ethanone O-benzyl-oxime

4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxamidine dihydrochloride salt

4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid 2-methyl-benzylamide

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-2-pyridin-3-yl-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

9-(4,5-Dimethyl-thiazol-2-yl)-4-(4-naphthalen-2-yl methyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

9-(4,5-Dimethyl-thiazol-2-yl)-4-(4-quinolin-2-ylmethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid 2-chloro-benzylamide

9-(4,5-Dimethyl-thiazol-2-yl)-4-[4-(2-thiophen-2-yl-ethyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid 2-methoxy-benzylamide

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5-methyl-6-phenyl-5H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-3(S)-methyl-piperazin-1-yl}-5,6,7,8

-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid methyl ester

4-(9-Cyano-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl)-piperazine-1-carboxylic acid phenylamide

9-(4,5-Dimethyl-thiazol-2-yl)-4-[4-(1-methyl-1H-indol-3-ylmethyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

4-[4-(2,3-Dihydro-benzo[1,4]dioxin-6-ylmethyl)-piperazin-1-yl]-9-(4,5-dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

3-(2-{4-[9-(4,5-Dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl]-piperazin-1-yl}-ethyl)-N,N-dimethyl-benzamide

4-(9-Cyano-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl)-piperazine-1-carboxylic acid ethylamide

4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid 2,3-dimethoxy-benzylamide

3-(2-{4-[9-(4,5-Dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl]-piperazin-1-yl}-ethyl)-benzamide

9-(4,5-Dimethyl-thiazol-2-yl)-4-(4-quinolin-4-ylmethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid 3-cyano-benzylamide

4-(4-Benzo[b]thiophen-3-ylmethyl-piperazin-1-yl)-9-(4,5-dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (pyridin-2-ylmethyl)-amide

9-(4,5-Dimethyl-thiazol-2-yl)-4-[4-(1H-indol-3-ylmethyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

4-({[4-(4-Phenethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonyl]-amino}-methyl)-benzoic acid methyl ester

4-(4-Benzofuran-2-ylmethyl-piperazin-1-yl)-9-(4,5-dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

4-(4-Benzo[1,3]dioxol-5-ylmethyl-piperazin-1-yl)-9-(4,5-dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

9-(4,5-Dimethyl-thiazol-2-yl)-4-[4-(1H-indol-5-ylmethyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

3-(2-{4-[9-(4,5-Dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl]-piperazin-1-yl}-ethyl)-N-methyl-benzamide

4-(4-Biphenyl-4-ylmethyl-piperazin-1-yl)-9-(4,5-dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

1-{4-[9-(4,5-Dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl]-piperazin-1-yl}-3-(quinolin-5-yloxy)-propan-2-ol

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid amide

9-(4,5-Dimethyl-thiazol-2-yl)-4-{4-[2-(4-methylsulfanyl-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid 2,3-dimethoxy-benzylamide

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid 4-methoxy-benzylamide

9-(4,5-Dimethyl-thiazol-2-yl)-4-{4-[2-(4-nitro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene; hydrochloride

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-2-o-tolyl-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-9-pyrimidin-2-yl-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

9-(4,5-Dimethyl-thiazol-2-yl)-4-[4-(3-phenoxy-benzyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

9-(4,5-Dimethyl-thiazol-2-yl)-4-(4-{2-[4-(pyrrolidine-1-sulfonyl)-phenyl]-ethyl}-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

4-(4-Phenoxymethyl-piperidin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

9-(4,5-Dimethyl-thiazol-2-yl)-4-[4-(3-phenyl-prop-2-ynyl)-piperazin-1-yl]-5,6,7,8-

tetrahydro-1,3,4b-triaza-fluorene

2-{4-[9-(4,5-Dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl]-piperazin-1-yl}-1-morpholin-4-yl-ethanone

9-(4,5-Dimethyl-thiazol-2-yl)-4-(4-pentyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid

2-{4-[9-(4,5-Dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl]-piperazin-1-yl}-acetamide

2-{4-[9-(4,5-Dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl]-piperazin-1-yl}-N-isopropyl-acetamide

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-6-ethyl-5-methyl-5H-pyrrolo[3,2-d]pyrimidine-7-carboxylic acid amide

2-(4-{4-[9-(4,5-Dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl]-piperazin-1-ylmethyl}-phenoxy)-N,N-dimethyl-acetamide

9-(4,5-Dimethyl-thiazol-2-yl)-4-[4-(5-pyridin-2-yl-thiophen-2-ylmethyl)-piperazin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

4-(4-Benzothiazol-2-ylmethyl-piperazin-1-yl)-9-(4,5-dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (6-methyl-pyridin-3-yl)-amide

9-(4,5-Dimethyl-thiazol-2-yl)-4-(4-quinolin-3-ylmethyl-piperazin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

2-{4-[9-(4,5-Dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl]-piperazin-1-yl}-N-(3,4,5-trimethoxy-phenyl)-acetamide

2-{4-[9-(4,5-Dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl]-piperazin-1-yl}-N-(3-nitro-phenyl)-acetamide

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (pyridin-3-ylmethyl)-amide

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid phenethyl-amide

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (pyridin-2-ylmethyl)-amide

2-{4-[9-(4,5-Dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl]-piperazin-1-yl}-N-(1H-pyrazol-3-yl)-acetamide

2-(4-{4-[9-(4,5-Dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl]-piperazin-1-ylmethyl}-phenoxy)-1-morpholin-4-yl-ethanone

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid 4-dimethylamino-benzylamide

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid 2-pyrrolidin-1-yl-benzylamide

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (2,2-dimethyl-propyl)-amide

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid 2-morpholin-4-yl-benzylamide

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid 2,4-dimethoxy-benzylamide

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid 2-(4-methyl-piperazin-1-yl)-benzylamide

4-[4-(6,7-Difluoro-quinolin-2-ylmethyl)-piperazin-1-yl]-9-(4,5-dimethyl-thiazol-2-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (benzo[1,3]dioxol-4-ylmethyl)-amide

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid isobutyl-amide

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (quinolin-2-ylmethyl)-amide

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (quinolin-4-ylmethyl)-amide

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (3-nitro-phenyl)-amide

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-

fluorene-9-carboxylic acid 2,6-dimethoxy-benzylamide

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (3-methoxy-phenyl)-amide

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid pyridin-3-ylamide

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid phenylamide

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid pyridin-2-ylamide

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid pyridin-4-ylamide

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (3-dimethylamino-phenyl)-amide

4-(4-Phenethyl-piperazin-1-yl)-9-pyrimidin-2-yl-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid ethylamide

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6-dimethyl-5H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-6,7,8,9-tetrahydro-5H-1,3,4b-triaza-benzo[a]azulene-10-carbonitrile

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-6,7,8,9-tetrahydro-5H-1,3,4b-triaza-benzo[a]azulene-10-carboxylic acid amide

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6-dimethyl-5H-pyrrolo[3,2-d]pyrimidine-7-carboxylic acid amide

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-2,3-dihydro-1H-3a,5,7-triaza-cyclopenta[a]indene-8-carboxylic acid amide

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid propylamide

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (4-methyl-pyridin-3-yl)-amide

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid pyrimidin-5-ylamide

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (5-bromo-pyridin-3-yl)-amide

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (6-methoxy-pyridin-3-yl)-amide

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid isoquinolin-4-ylamide

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid quinolin-3-ylamide

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (5-pyrrolidin-1-yl-pyridin-3-yl)-amide

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carboxylic acid (6-methyl-pyridin-2-ylmethyl)-amide

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-2,3-dihydro-1H-3a,5,7-triaza-cyclopenta[a]indene-8-carboxylic acid ethylamide

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-6,7,8,9-tetrahydro-5H-1,3,4b-triaza-benzo[a]azulene-10-carboxylic acid ethylamide

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-6-isopropyl-5-methyl-5H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile

4-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-6-ethyl-5-methyl-5H-pyrrolo[3,2-d]pyrimidine-7-carbonitrile

4-Morpholin-4-yl-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

4-Pyrrolidin-1-yl-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

4-(Methyl-phenethyl-amino)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

4-(4-Hydroxy-4-phenyl-piperidin-1-yl)-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

4-[(3-Dimethylamino-propyl)-methyl-amino]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

4-[(2-Cyano-ethyl)-methyl-amino]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

4-[(9-Cyano-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl)-methyl-amino]-butyric acid

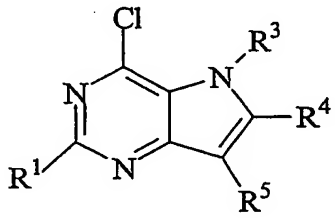
1-(9-Cyano-5,6,7,8-tetrahydro-1,3,4b-triaza-fluoren-4-yl)-piperidine-4-carboxylic acid phenylamide

4-[4-(Benzyl-methyl-amino)-piperidin-1-yl]-5,6,7,8-tetrahydro-1,3,4b-triaza-fluorene-9-carbonitrile

and the pharmaceutically acceptable salts thereof.

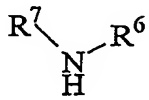
5. A pharmaceutical composition which comprises a pharmaceutically acceptable carrier or diluent and, as an active ingredient, a compound as defined in any one of claims 1 to 4.

6. A process for producing a compound as defined in claim 1, which process comprises treating a compound of formula (II):



(II)

wherein R^1, R^3, R^4 and R^5 are as defined in claim 1, with a compound of formula (III)



wherein R^6 and R^7 are as defined in claim 1, in an organic solvent in the presence of a base.

7. A compound as defined in any one of claims 1 to 4 for use in a method of medical treatment of the human or animal body by therapy.

8. A compound as claimed in claim 7 for use as an inhibitor of MRP or as an LTC_4 efflux inhibitor.

9. A compound as claimed in claim 7 or 8 for use as a modulator of multidrug resistance, in potentiating the cytotoxicity of a chemotherapeutic agent, in treating a multi-drug resistant tumour or in enhancing the net absorption, distribution, metabolism or elimination characteristics of a therapeutic agent, in treating inflammation or bronchoconstriction, in treating HIV infection, in treating pneumonia or in treating a patient suffering from epilepsy.

10. Use of a compound as defined in claim 1 in the manufacture of a medicament for use as an inhibitor of MRP or as an LTC_4 efflux inhibitor.

11. Use according to claim 10 wherein the medicament is for use as an inhibitor of MRP1.

12. Use of a compound as defined in claim 1 in the manufacture of a medicament for use as a modulator of multidrug resistance, in potentiating the cytotoxicity of a chemotherapeutic agent, in potentiating the therapeutic effect of a drug directed against a multidrug resistant pathogen, in treating a multi-drug resistant tumour or in enhancing the net absorption, distribution, metabolism or elimination characteristics of a therapeutic agent, in treating asthma or other respiratory disease, in treating HIV infection, in treating pneumonia or in treating a patient suffering from epilepsy.

13. A method of treating a patient in need of an inhibitor of MRP, which method comprises administering thereto a compound as defined in claim 1.

14. A method of modulating MRP mediated MDR in the treatment of a tumour, which method comprises administering to a patient harbouring a tumour which expresses MRP mediated MDR a therapeutically effective amount of a compound as defined in any one of claims 1 to 4.

15. A method of potentiating the cytotoxicity of an agent which is cytotoxic to a tumor cell, which method comprises administering to a patient in need thereof a therapeutically effective amount of a compound as defined in any one of claims 1 to 4.

INTERNATIONAL SEARCH REPORT

GB2004/000274

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 A61K31/437 A61P43/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97/34897 A (JANSSENS FRANS EDUARD ;SOMMEN FRANCOIS MARIA (BE); JANSSEN PHARMAC) 25 September 1997 (1997-09-25) claim 1	1-15

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 May 2004	03/06/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Wolf, C

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

PCT/GB2004/000274

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 13-15
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 13-15 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box II.1

Claims Nos.: 13-15

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

GB2004/000274

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